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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

NOTICE OF MOTION AND MOTION BY DEFENDANT VYSIS, INC. FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

Date: July 30, 2001
Time: 10:30 am
Dept.: Courtroom 1

TO ALL PARTIES AND THEIR COUNSEL OF RECORD:

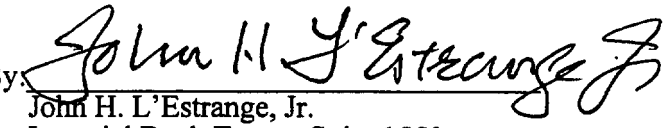
PLEASE TAKE NOTICE that on July 30, 2001, or as soon thereafter as this matter may be heard before the Honorable Marilyn Huff in Courtroom 1 of the above entitled court located at the United States Courthouse, 940 Front Street, San Diego, California, 92101, defendant Vysis, Inc. ("Vysis") will and hereby does move the Court to enter final judgment against it on Counts I and III

of plaintiff Gen-Probe, Incorporated's Second Amended Complaint pursuant to Rule 54(b) of the Federal Rules of Civil Procedure.

This Motion is based on this Notice of Motion and Motion, the accompanying Memorandum of Points and Authorities, the Declaration of Thomas W. Banks, and on such other and further oral and documentary evidence as the Court may consider at the time of hearing.

Dated: June 29, 2001

WRIGHT & L'ESTRANGE

By: 

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SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

Case No.: 99CV 2668H (AJB)

CERTIFICATE OF PERSONAL SERVICE

I, the undersigned, declare: I am over the age of eighteen years and not a party to the cause; I am employed in, or am a resident of, the County of San Diego, California, and my business address is: 4665 Park Blvd., San Diego, California 92116.

On June 29, 2001, I served the following document(s):

///

///

1. **NOTICE OF MOTION AND MOTION BY DEFENDANT VYSIS, INC. FOR ENTRY OF FINAL JUDGEMENT UNDER RULE 54(b)**

2. **MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF VYSIS' MOTION FOR ENTRY OF JUDGMENT UNDER RULE 54(b)**

3. **DECLARATION OF THOMAS W. BANKS IN SUPPORT OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)**

by personally serving copies of said documents upon the following individuals at the following addresses or by leaving copies at the office listed below, in an envelope or package clearly labeled to identify the person being served, with a receptionist or, with a person having charge thereof:

Patrick Maloney
Stephen P. Swinton
COOLEY GODWARD, LLP
4365 Executive Drive, #1100
San Diego, CA 92121-2128

R. William Bowen, Jr.
GEN-PROBE INCORPORATED
10210 Genetic Center Drive
San Diego, CA 92121-4362

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Executed on June 29, 2001 in San Diego, California.

DIVERSIFIED LEGAL SERVICES, INC.

By_____

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

Date: July 30, 2001
Time: 10:30 am
Dept.: Courtroom 1

On June 19, 2001, this Court granted Gen-Probe's motion for partial summary judgment under Counts One and Three of its Second Amended Complaint that its nucleic acid test for human immunodeficiency virus ("HIV") and hepatitis C virus ("HCV") does not literally infringe the claims of Vysis' U.S. Patent No. 5,750,338 ("the '338 patent"). In granting Gen-Probe's motion, the Court construed the claims of the '338 patent as encompassing only non-specific amplification methods.

Vysis has carefully reviewed the Court's ruling and concludes that (1) the Court erred in construing the claims more narrowly than their legally correct scope, (2) Vysis has no reasonable expectation of prevailing at trial on the issue of infringement if the Court's claim construction is sustained, and (3) any attempt to resolve patent validity and enforceability issues using the Court's narrow claim construction will be a waste of resources of the Court and the parties. If Vysis is correct and the claims are determined by the Federal Circuit to be of broader scope, the validity and enforceability issues will have to be retried. If Vysis is incorrect and the Court's narrow claim construction is sustained on appeal, there will be no need to try the validity and enforceability issues at all. Accordingly, Vysis seeks entry of final judgment against it on Counts I and III of Gen-Probe's Second Amended Complaint pursuant to Rule 54(b), Fed. R. Civ. P. and a stay of all remaining proceedings, so that it may pursue an immediate appeal of this core claim construction issue to the Federal Circuit.

I. Entry of Final Judgment is Appropriate

When a lawsuit involves multiple claims for relief, Rule 54(b) permits the Court to enter final judgment as to fewer than all of the counts upon an express determination that there is no just reason for delay. Fed. R. Civ. P. 54(b).[1] As no just reason for delay exists here, this case is a perfect candidate for entry of final judgment as to Gen-Probe's Counts I and III.[2]

A. The Court's Summary Judgment Ruling is Dispositive

The Court's claim construction and summary judgment grant, if sustained on appeal, are finally dispositive of Count I of Gen-Probe's Second Amended Complaint. Moreover, although the Court did not make an express declaration of Gen-Probe's rights and obligations under its license with Vysis, the Court's holding that Gen-Probe's HIV/HCV test kit does not infringe the claims of

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[1] Fed. R. Civ. P. 54(b) uses the term "claim" to refer to a "claim for relief." To avoid confusion between the different usages of the word "claim" in civil procedure and patent law, this Memorandum will, unless otherwise indicated, use the term "count" to refer to a "claim for relief" and the term "claim" to refer to the claim of a patent.

[2] Count I of Gen-Probe's Second Amended Complaint alleged that its HIV and HCV test kits do not infringe the claims of the '338 patent. Count III sought a declaration of Gen-Probe's rights and obligations under its license with Vysis. Second Amended Complaint, ¶¶ 27-28, 31-33 (attached as Exhibit A to the Declaration of Thomas W. Banks in Support of Vysis' Motion for Entry of Judgment Under Rule 54(b) ("Banks Decl.").)

the '338 patent, if sustained on appeal, necessarily disposes of Count III.[3] The basic foundation of Gen-Probe's lawsuit is "the nature and scope of any obligation of [Gen-Probe] to make royalty payments to [Vysis]" pursuant to the parties' '338 patent license agreement. (Gen-Probe Second Amended Complaint, ¶ 1 (Banks Decl. Exhibit A).) The Court's summary judgment ruling effectively resolves this issue.

B. Trial of the Invalidity and Unenforceability Counts Will be Wasteful

The Court's summary judgment of noninfringement necessarily resolves Gen-Probe's rights and obligations under the '338 license. Accordingly, there is nothing further for Gen-Probe to gain by trying the issues of invalidity (Count II) and unenforceability (Counts V and VI). Indeed, proceeding with trial of those issues after ruling on summary judgment that there is no infringement as a matter of law would effectively result in rendition of an impermissible advisory opinion concerning the validity and enforceability of the '338 patent.

Moreover, the Court's claim construction ruling is central to and will affect the discovery and trial of all of the patent issues remaining in this case. Gen-Probe has asserted that the claims of the '338 patent are anticipated under 35 U.S.C. § 102 and obvious under 35 U.S.C. § 103. Resolving each of these issues will require comparing the *claimed* invention against the prior art. *See, e.g., SIBIA Neurosciences Inc. v. Cadus Pharmaceutical Corp.* 225 F.3d 1349, 1355 (Fed. Cir. 2000) ("The first step in any invalidity analysis is claim construction, an issue of law that this court reviews *de novo*"); *Key Pharmaceuticals v. Hercon Labs. Corp.*, 161 F.3d 709, 714 (Fed. Cir. 1998) ("not unlike a determination of infringement, a determination of anticipation, as well as obviousness, involves two steps. First is construing the claim, a question of law for the court, followed by, in the case of anticipation or obviousness, a comparison of the construed claim to the prior art.")

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[3] Gen-Probe's summary judgment motion notes that "the terms of the license impose obligations only upon those products of Gen-Probe that would constitute an infringement of the '338 patent but for the license." Memorandum of Points and Authorities in Support of Plaintiff Gen-Probe Incorporated's Motion for Partial Summary Judgment at 2 n.2 (attached as Banks Decl. Exhibit B).

The same is true with respect to Gen-Probe's unenforceability allegations. The question of the materiality of alleged misrepresentations or omissions is resolved with reference to the scope of the invention claimed. *See* 37 C.F.R. 1.56; *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1457 (Fed. Cir. 1984) (resolving issues of inequitable conduct requires reference to the claims of the patent).

A dramatic waste of judicial resources (as well as the time and resources of the parties, witnesses, and the jury) would result if the validity and enforceability issues were tried based on a construction of the claims of the '338 patent that was later reversed by the Federal Circuit. If these issues were tried and the Federal Circuit were to subsequently construe the claims more broadly, the trial of the validity and enforceability issues will have been for naught – and these issues would have to be tried anew. Moreover, fact discovery is still ongoing in this case, and expert discovery has yet to begin. Trial is over six months away. To the extent the parties may narrow their discovery and restrict their theories of the case as a result of this Court's claim construction, a different construction by the Federal Circuit may well require further fact discovery and additional expert discovery beyond that which would be needed if this Court's claim construction were upheld.

Rather than risk duplicative discovery and the possibility of a trial that would be rendered meaningless should the Federal Circuit have a different claim construction, it would be far more efficient to obtain appellate review now, prior to trying the remaining issues of the case.[4] Indeed, the very issue of efficiency was recognized by Judge Rader, of the Court of Appeals for the Federal Circuit, sitting by designation as the trial judge in *Loral Fairchild Corp. v. Victor Co.*, 931 F. Supp. 1044 (E.D.N.Y. 1996), *aff'd* 181 F.3d 1313 (1999). In *Loral*, Judge Rader directed entry of final judgment under Rule 54(b) of his own judgment of noninfringement, holding that

> [T]his court's claim construction drove the resolution of the issues between Sony and Loral. Claim construction impacted significantly on this court's conclusions on literal and equivalents infringement on both patents. Currently, the Federal Circuit does not defer to trial

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[4] Claim construction is a matter of law that the Federal Circuit reviews *de novo*. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1456 (Fed. Cir. 1998) (en banc).

> court judgments on claim construction. . . . Thus, the Federal Circuit may adopt a different view of the claims at issue. With a number of trials remaining, the Federal Circuit's guidance on the proper scope of the claims will clarify the parties' rights and obligations under the patents and may lead to a substantial savings of time and expense.

Loral, 931 F. Supp. at 1047-48 (citations omitted). Although *Loral* involved multiple parties rather than multiple claims for relief, Judge Rader's rationale for entry of judgment under Rule 54(b) is equally applicable to this case.

C. The Remaining Counts Are Separable from the Adjudicated Counts

The Supreme Court has held that in deciding whether there are no just reasons for delay, a district court may consider whether the adjudicated counts are separable from the counts yet to be decided, and whether the nature of the adjudicated counts is such that the appellate court would not have to decide the same issues more than once. *Curtiss-Wright Corp. v. General Elec. Co.*, 446 U.S. 1 (1980). Here, the remaining counts are separable, and failure to obtain a prompt determination of the proper scope of the claims is more likely to result in multiple reviews of the same issues by the appellate court.

Apart from the fundamental issue of claim construction, Gen-Probe's invalidity and unenforceability counts are legally and factually distinct from its noninfringement count. While the noninfringement issue was resolved by comparing Gen-Probe's HIV/HCV test with the construed claims, resolving the invalidity Count II will require comparing the claims against the prior art. The unenforceability Counts V and VI will require examining the actions of the patent owner during the prosecution of the '338 patent. Because these counts do not share common legal or factual bases with the adjudicated issue of noninfringement (other than the core issue of claim construction), they are properly separable from the noninfringement count.

The case is even clearer for Gen-Probe's Count IV for unfair competition. This cause of action, brought under California law, is based solely on Vysis' actions *subsequent* to the issuance of the '338 patent. Moreover, Gen-Probe only asserts Vysis' knowledge of the purported invalidity and unenforceability of the '338 patent as the predicate for its unfair competition claim – the presence or absence of infringement has nothing to do with this count. Accordingly, the unfair competition count is similarly separable from the noninfringement count.

II. A Stay of Proceedings on the Remaining Counts is Appropriate

As demonstrated above, the Federal Circuit's *de novo* claim construction will settle the fundamental issue upon which the remainder of this case will rest. So that the Court and the parties may conserve their resources and otherwise avail themselves of the efficiencies created by an immediate appeal to the Federal Circuit, the Court should stay proceedings on Gen-Probe's remaining counts pending appellate review.

Gen-Probe cannot complain of prejudice in connection with the requested stay. If Gen-Probe is correct in the claim construction it has persuaded the Court to adopt, the most expeditious way of getting a final resolution of its obligations under the '338 license is to have the claim construction issue promptly reviewed by the Federal Circuit.

Finally, there is ample precedent for the requested stay. *See, e.g., Trilogy Comms. Inc. v. Times Fiber Comms., Inc.*, 109 F.3d 739 (Fed. Cir. 1997), in which the Federal Circuit noted that

> having resolved the infringement claim, the [district] court certified the summary judgment of non-infringement as an appealable final judgment pursuant to Fed. R. Civ. P. 54(b). The court stayed further proceedings on Times Fiber's counterclaims, including its claim for a declaratory judgment of patent invalidity and unenforceability.

Id. at 741.

III. Conclusion

For the foregoing reasons, no just reason for delay exists. Accordingly, entry of final judgment as to Counts I and III of Gen-Probe's Second Amended Complaint is appropriate.

Dated: June 29, 2001

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

DECLARATION OF THOMAS W. BANKS IN SUPPORT OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

Date: July 30, 2001
Time: 10:30 am
Dept.: Courtroom 1

I, Thomas W. Banks, declare and state as follows:

1. I have personal knowledge of the facts set forth in this declaration.

2. I am an attorney licensed to practice in the State of California and admitted to practice in the United States District Court for the Southern District of California. I am a partner at

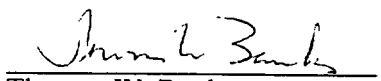
the law firm of Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., and represent Defendant Vysis, Inc. ("Vysis") in this litigation.

3. Attached as Exhibit A to this declaration is a true and correct copy of Gen-Probe's Second Amended Complaint.

4. Attached as Exhibit B to this declaration is a true and correct copy of Gen-Probe's Memorandum of Points and Authorities In Support of Plaintiff Gen-Probe Incorporated's Motion for Partial Summary Judgment.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge and belief.

Executed this 28th day of June, 2001 at Palo Alto, California.



Thomas W. Banks

Exhibit	Description	Page
A	Gen-Probe's Second Amended Complaint.	1
B	Gen-Probe's Points and Authorities In Support of Plaintiff Gen-Probe Incorporated's Motion for Partial Summary Judgment.	24

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC., Defendant.	No. 99CV2668H AJB **SECOND AMENDED COMPLAINT FOR DECLARATORY RELIEF AND UNFAIR COMPETITION**

PLAINTIFF GEN-PROBE ALLEGES:

INTRODUCTION

1. This action concerns the nature and scope of any obligation of plaintiff Gen-Probe Incorporated ("Gen-Probe") to make royalty payments to defendant Vysis, Inc. ("Vysis") pursuant to a patent license agreement between the parties ("the License") in light of the invalidity and non-infringement of United States Patent No. 5,750,338 ("the '338 patent") that is a subject of that

License. As set forth below, Gen-Probe asks this Court to declare the '338 patent invalid and further to declare that Gen-Probe's current and anticipated activities do not infringe any valid claims of the '338 patent. As a corollary to those declarations, Gen-Probe also asks this court to declare its rights and obligations under the terms of the parties' License. Finally, Gen-Probe also seeks relief from Vysis' continuing acts of wrongful and unfair conduct with respect to the '338 patent.

THE PARTIES

2. Gen-Probe was founded in San Diego in 1984 as a small "start up" company, seeking to develop products based on the discoveries of a local research scientist. Over time, Gen-Probe became one of the largest biotechnology firms in San Diego. Gen-Probe now maintains its principal offices and research facilities at 10210 Genetic Center Drive in San Diego, where it employs over 500 scientists and staff. Gen-Probe is organized under the laws of the State of Delaware.

3. Gen-Probe is informed and believes that defendant Vysis, Inc. (hereinafter "Vysis" or "the defendant") is a corporation organized and incorporated under the laws of the State of Delaware. Gen-Probe is further informed and believes that Vysis maintains its principal place of business in Downers Grove, Illinois and that it is controlled by BP Amoco, Inc.

JURISDICTION AND VENUE

4. Counts One and Two of this Complaint seek declaratory relief under the Declaratory Judgment Act, Title 28, United States Code, Sections 2201 and 2202. This Court has subject matter jurisdiction of the claims asserted thereunder by reason of Title 28, United States Code, Sections 1331, 1338(a), 1338(b) and 1367.

5. Venue is proper in this District under Title 28, United States Code, Sections 1391(b) and 1400(b).

BACKGROUND

6. Living cells store genetic information in molecules of nucleic acid known as DNA. These molecules consist of long, thin, chain-like strands which, in turn, are usually found in the form of two tightly bound, complementary chains. DNA molecules retain their genetic information

in the form of a genetic code. The information in the DNA determines the life processes of each organism. The information in the DNA is used to make related nucleic acid molecules called RNA that cells use to manufacture proteins.

7. Through the work of its scientists and staff, Gen-Probe has developed and continues to develop diagnostic tests that seek out the DNA or RNA of the infectious organisms. These types of tests are generally referred to as "genetic probes" or "nucleic acid tests" ("NAT"). Gen-Probe now markets DNA probe products that test for a wide range of microorganisms that cause tuberculosis, strep throat, pneumonia, fungal infections and sexually transmitted diseases. Through the efforts of its scientists and staff, Gen-Probe has emerged as the recognized world leader in the development, manufacture and commercialization of diagnostic products based on its patented genetic probe technology. Gen-Probe has received over 40 FDA clearances and approvals for genetic probe tests to detect a wide range of microorganisms, including Chlamydia trachomatis, Mycobacterium tuberculosis and Neisseria gonorrhoeae.

8. Many human diseases are caused by bacterial or viral agents that invade living cells. Historically, the presence of these bacterial or viral agents was detected directly by time-consuming methods such as culture or indirectly through the detection of antibodies. Unfortunately, it takes time, sometimes weeks or months, to grow organisms in culture, and it usually takes months for the body to manufacture antibodies in sufficient amounts to reveal the presence of infectious agents. Consequently, these methods do not lend themselves to early detection of infection. NAT addresses this problem.

9. Among the disease detection technologies recently applied by Gen-Probe is its patented nucleic acid technology known as "Transcription-Mediated Amplification" ("TMA"). This technology enables Gen-Probe's NAT products to detect extraordinarily small quantities of the nucleic acids of infectious agents.

10. In September 1996, Gen-Probe received a $7.7 million grant from the National Institutes of Health to develop TMA-based nucleic acid tests to be used in screening donated blood for and human immunodeficiency virus (HIV), the causative agent of AIDS, and hepatitis C virus (HCV), which causes a severe form of hepatitis.

11. At the time of the NIH grant to Gen-Probe, donated blood was principally tested by procedures that detected the presence of antibodies to the viruses being screened. Due to the time it takes for the body to make antibodies after initial infection, donated blood may test negative for antibodies, yet still carry infectious viruses. This delay between the time of actual infection and the time that antibodies can first be detected is often known as the "window period." Reduction of this "window period" was a significant concern of the United States government and the primary focus of the grant to Gen-Probe to develop NAT diagnostics for use in blood screening.

12. In fulfilling its obligations under the grant, Gen-Probe developed NAT tests to detect the DNAs of HIV and hepatitis C in blood. Through the use of its NAT test, Gen-Probe believes that researchers and medical personnel may rapidly and *directly* detect the presence of genetic material of viruses like HIV and HCV more accurately and without the complications and delay associated with conventional *indirect* tests. As such, Gen-Probe believes that its new test may significantly reduce the "window period" for detection of these extremely harmful viral agents and resulting diseases.

13. Final development of the NAT tests for blood screening in the United States is now taking place in testing conducted by the American Red Cross, America's Blood Centers, and others. ("A Purity Quest; Local Biotech's Ultra-Sensitive Blood Screening Could Cut Risk of AIDS, Hepatitis," *San Diego Union*, March 25, 1999, page C-1.) Use of the tests in the United States is made pursuant to an Investigational New Drug Application filed with the United States Food and Drug Administration. In blood tested by the American Red Cross, Gen-Probe's products have detected hepatitis C and HIV which escaped detection by prior methods. ("New Blood Screening Finds Virus Others Missed; Experimental Test Turns Up Hepatitis C In Donated Blood," *San Diego Union*, April 2, 1999, page B-2.)

14. On September 21, 1999, the French Ministry of Health approved the sale of the Gen-Probe blood screening tests in France. Gen-Probe anticipates approval of its tests for us in Australia in early 2000.

15. Gen-Probe has entered into an agreement with Chiron Corporation ("Chiron") of Emeryville, California, with respect to the development, manufacture, and distribution of blood

screening products. Gen-Probe is also a party to an agreement with Bayer Corporation ("Bayer") of Emeryville, California with respect to the development, manufacture, and distribution of clinical diagnostic products for the detection of HIV and hepatitis C, among other pathogens.

16. Gen-Probe anticipates that additional clinical trials in the United States of its HIV/HCV tests for use in blood screening and in clinical diagnostics will commence in the first part of 2000. Gen-Probe anticipates the conclusion of those clinical trials, and the initiation of commercial sales in the United States of kits containing its HIV/HCV blood screening test, during 2000.

17. All of the Gen-Probe products are manufactured in San Diego, California.

THE '338 PATENT

18. Gen-Probe is informed and believes that on or about May 12, 1998, the United States Patent and Trademark Office issued United States Patent No. 5,750,338 ("the '338 patent") based upon Patent Application No. 238,080 filed on May 3, 1994.

19. Gen-Probe is informed and believes that defendant Vysis claims to be the owner, by assignment, of the entire right, title and interest of the '338 patent. The claims of the '338 patent purport to relate to assays and probes for polynucleotide molecules such as DNA and RNA.

20. In early 1999, Vysis informed Gen-Probe that it believed that the '338 patent "applied" to Gen-Probe's NAT blood screening tests for HIV and HCV. Following further discussions and to avoid any complications in Gen-Probe's plans for commercial deployment of its NAT test kits, as of June 22, 1999 Gen-Probe obtained a license ("the License") from Vysis under the '338 patent. Gen-Probe also obtained options to the License for its relationships with Chiron and Bayer.

21. Under the terms of the License, Vysis requires Gen-Probe (and its allied parties if the options are exercised) to make significant financial payments to Vysis as royalties on the sale of any product covered by any valid claims of the '338 patent.

22. Notwithstanding the existence of the License, and as further alleged herein, Gen-Probe believes that the claims of '338 patent are invalid in all material respects. Furthermore, Gen-Probe believes that its NAT blood screening tests do not infringe any valid claim of the '338 patent.

As such, Gen-Probe disagrees with Vysis' contention that the claims of the '338 patent "apply" to Gen-Probe's activities and contemplated products. For these same reasons, Gen-Probe contends that it has no obligation to make any royalty payments to Vysis with respect to its present products and activities and any contemplated products and activities that Vysis may later claim infringe the claims of the '338 patent.

23. Gen-Probe has communicated to Vysis its belief that the claims of the '338 patent are invalid. In support of that belief, Gen-Probe has provided Vysis with information that demonstrates that the claims of the '338 patent are invalid. Gen-Probe has also advised Vysis of its belief that its NAT test kits for use in detecting HCV and HIV in the Nation's blood supply do not and will not infringe any valid claims of the '338 patent.

24. Notwithstanding its receipt of the foregoing information, Vysis persists in its assertion that the claims of the '338 patent are valid and enforceable and that Gen-Probe is obligated to make royalty payments in accordance with the terms of the License.

25. Based upon a long history of litigation between Gen-Probe and Vysis and its affiliates, Gen-Probe reasonably anticipates that should it fail to pay royalties pursuant to the License, Vysis will aggressively attempt to enforce its perceived rights under both the License and the '338 patent by terminating the License and by initiating litigation against Gen-Probe, its allied parties, and customers.

26. An actual case or controversy exists between Gen-Probe and Vysis concerning the validity and infringement of the '338 patent and Gen-Probe's rights and obligations under the License. The determination of the issues presented in this complaint will inure to the greater public benefit and good.

COUNT ONE

NON-INFRINGEMENT OF THE '338 PATENT

27. Gen-Probe repeats, repleads and incorporates herein the allegations of paragraphs 1 through 26 of this complaint.

28. Gen-Probe's NAT test kits for use in detecting HCV and HIV in the Nation's blood supply do not and will not infringe any valid claims of the '338 patent.

COUNT TWO

INVALIDITY OF THE '338 PATENT

29. Gen-Probe repeats, repleads and incorporates herein the allegations of paragraphs 1 through 26 of this complaint.

30. The claims of the '338 patent are invalid by reason of one or more provisions of Title 35 of the United States Code.

COUNT THREE

DECLARATORY RELIEF

31. Gen-Probe repeats, repleads and incorporates herein the allegations of paragraphs 1 through 26 of this complaint.

32. An actual controversy has arisen and now exists concerning the rights and obligations of Gen-Probe pursuant to the terms of the parties' License. Those disputes arise from and their resolution depends upon the federal patent laws.

33. Gen-Probe seeks a declaration of its rights and obligations under the License, particularly in light of the invalidity and non-infringement of the '338 patent and defendant's acts of unfair competition as alleged herein.

COUNT FOUR

UNFAIR COMPETITION

34. Gen-Probe repeats, repleads and incorporates herein the allegations of paragraphs 1 through 33 of this complaint.

35. Vysis knows or should know the underlying facts establishing the invalidity and/or unenforceability of the claims of the '338 patent. In continuing to enforce the claims of the '338 patent, Vysis has acted and continues to act unfairly, inequitably and in bad faith. In addition, Vysis' actions constitute unlawful, unfair or fraudulent business practices under California Business & Professions Code Sections 17200, *et seq.*

36. By reason of the aforementioned acts of unfair competition and unlawful, unfair and fraudulent business practices, Gen-Probe is entitled to damages, as established at time of trial, restitution and injunctive relief.

COUNT FIVE

UNENFORCEABILITY OF THE '338 PATENT

37. Gen-Probe repeats, repleads and incorporates herein the allegations of paragraphs 1 through 36 of this complaint.

38. Applicants for patents have a general duty of candor and good faith in their dealings with the Patent and Trademark Office (the "Patent Office") and an affirmative obligation to disclose to the Patent Office all information that they know to be material to the examination of a pending application pursuant to 37 C.F.R. § 1.56. This duty extends to the applicants and their representatives, such as their attorneys, and all others associated with the prosecution, including every person who is substantively involved in the preparation or prosecution of the application.

39. Gen-Probe is informed and believes, and thereon alleges, that Vysis or its predecessors-in-interest and their agents (hereinafter collectively referred to as "the applicants") knowingly and willfully concealed and misrepresented material evidence during the prosecution of the '338 patent applications and that by such inequitable conduct, the '338 patent is unenforceable against Gen-Probe for the reasons that follow.

FACTS RELATED TO THE ABANDONMENT OF THE CLAIMED INVENTION OF NUCLEIC ACID AMPLIFICATION

40. On October 23, 1986, the applicants filed a patent application entitled "Target and Background Capture Methods and Apparatus for Affinity Assays." After filing, the Patent Office assigned that application the numerical designation, Serial No. 06/922,155 (the "'155 application"). Although, the '155 application purported to describe a technique for reversible target capture, it contained no disclosure of or claims to amplification techniques as claimed by Vysis in the '338 patent. The applicants identified Mark L. Collins as the sole inventor of the alleged inventions claimed in the '155 application.

41. On December 21, 1987, prior to substantive examination of the '155 application by the Patent Office, Vysis filed a Continuation-in-Part of the '155 application. The Patent Office assigned this Continuation-in-Part application Serial No. 07/136,920 (the "'920 application"). The applicants entitled the '920 application "Target and Background Capture Methods with

Amplification," and initially submitted claims in the '920 application to a method of nucleic acid amplification (claims 1-23), and a claim to an instrument for performing assays for target polynucleotides (claim 24).

42. In its initial examination of the '920 application, the Patent Office issued a restriction requirement because it deemed the claimed inventions of the amplification and instrument claims of the '920 application as distinct. In response to that restriction requirement, the applicants elected to proceed in the '920 application by prosecuting only the amplification claims (claims 1-23).

43. On July 20, 1990, following the applicants' election to proceed with only the amplification claims in the '920 application, the Patent Office issued an office action regarding that application by which it rejected all claims of the '920 application on prior art and other grounds of patentability. The Patent Office provided the applicants until October 20, 1990, with extensions available until January 20, 1991, to submit a substantive response to that office action.

44. Rather than prepare a substantive response to the July 20, 1990 office action, and in order to continue prosecuting claims to a method of nucleic acid amplification, on January 22, 1991, the applicants filed a continuing application from the '920 application. The Patent Office designated this continuing application as application Serial No. 07/644,967 (the "'967 application"). Concurrent with the filing of the '967 application, the applicants then expressly abandoned the '920 application.

45. On March 12, 1991, the Patent Office issued an office action for the '967 application by which it issued a final rejection of the claims submitted with that application. Pursuant to statute, the Patent Office provided the applicants with a shortened response period until June 12, 1992, with extensions available until September 12, 1992, to respond to this final rejection of the claims of the '967 application.

46. Again rather than prepare a substantive response to the March 12, 1992, office action, and in order to continue prosecuting claims to a method of nucleic acid amplification, on September 14, 1992, the applicants filed a continuation application to the '967 application. The Patent Office designated this further continuation application Serial No. 07/944,505 (the "'505

application"). Consistent with continuation practice and rules, the applicants presented only claims to a method of nucleic acid amplification the '505 application, all other claims having been withdrawn by prior election. Concurrent with their filing of the '505 application, the applicants then expressly abandoned the '967 application.

47. On November 5, 1992, the Patent Office issued an office action for the '505 application by which it issued a final rejection of the claims submitted with that application. Pursuant to statute, the Patent Office provided the applicants with a shortened response period until February 5, 1993, with extensions available until May 5, 1993, to respond to this final rejection of the claims of the '505 application.

48. With the applicants' express knowledge and awareness of the requirement to respond to the November 5, 1992, office action within the statutorily required time and the further knowledge of the consequences of abandonment arising from any failure to respond within that required time, applicants intentionally elected not to respond to the office action.

49. Consistent with Patent Office rules and procedures, following the applicants' failure to respond to the November 5, 1992, office action, on June 16,1993, the Patent Office sent a formal notice of abandonment of the '505 application to the applicants. Again, however, consistent with the applicants' intentional decision not to respond to the office action, the applicants intentionally determined not to respond to the notice of abandonment.

FACTS RELATED TO THE PROSECUTION OF THE ALLEGED INSTRUMENT INVENTION

50. Gen-Probe is informed and believes, and thereon alleges, that the applicants intentionally failed to respond to the November 5, 1992, office action rejecting the claims of the '505 application and further intentionally failed to respond to the June 16, 1993 notice of abandonment as a result of their decision to abandon the alleged invention directed to a method of nucleic acid amplification originally elected for prosecution in the '920, '967 and '505 applications.

51. On January 31, 1991, consistent with the applicants' decision to acquiesce to the Patent Office's July 20, 1990, restriction requirement issued with respect to the distinct claimed inventions that applicants presented in the '920 application, the applicants filed a separate application by which they elected to prosecute only instrument-related claims originally presented

as claim 24 of the '920 application. The Patent Office assigned this instrument application Serial No. 07/648,468 (the "'468 application"). As originally filed and consistent with the restriction requirement, in the '468 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides. The applicants entitled the '468 application "Closed Vessel for Isolating Target Molecules and for Performing Amplification."

52. Through their '468 application, the applicants claimed priority of their instrument invention as a continuation-in-part application to the '920 and earlier '155 applications. However, applicants' claim to priority to the '920 and '155 applications was defective as it violated the requirement that the '468 application have been filed prior to the abandonment of the priority applications. In this case, although the applicants filed the '468 application on January 31, 1991, they intentionally abandoned the '920 application on January 22, 1991 and intentionally abandoned the '155 application on February 3, 1990. The applicants intentionally failed to disclose this lack of co-pendency of the '468 application during the prosecution of the '468 application.

53. The Patent Office initially rejected all the claims of the '468 application on prior art and other grounds of patentability in an office action mailed March 18, 1992. The Patent Office provided the applicants until June 18, 1992, with extensions available until September 18, 1992, to submit a substantive response to that office action.

54. Rather than prepare a substantive response to the March 18, 1992 office action, and in order to continue prosecuting claims to an instrument for performing assays for target polynucleotides, on September 17, 1992, the applicants filed a continuing application from the '468 application. The Patent Office designated this continuing application as application Serial No. 07/946,749 (the "'749 application"). Consistent with the restriction requirement originally issued in the '920 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides in the '749 application. Concurrent with the filing of the '749 application, the applicants then expressly abandoned the '468 application.

55. The Patent Office initially rejected all the claims of the '749 application on prior art and other grounds of patentability in an office action mailed March 22, 1993. The Patent Office provided the applicants until June 22, 1993, with extensions available until September 22, 1993, to

submit a substantive response to that office action.

56. Rather than prepare a substantive response to the March 22, 1993 office action, and in order to continue prosecuting claims to an instrument for performing assays for target polynucleotides, on September 21, 1993, the applicants filed a continuing application from the '749 application. The Patent Office designated this continuing application as application Serial No. 08/124,826 (the "'826 application"). Consistent with the restriction requirement originally issued in the '920 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides in the '826 application. Concurrent with the filing of the '826 application, the applicants then expressly abandoned the '749 application.

57. The Patent Office initially and finally rejected all the claims of the '826 application on prior art and other grounds of patentability in an office action mailed December 9, 1993. The Patent Office provided the applicants until March 9, 1994, with extensions available until June 9, 1994, to submit a substantive response to that office action.

58. Rather than prepare a substantive response to the December 9, 1993 office action, and in order to continue prosecuting claims to an instrument for performing assays for target polynucleotides, on June 8, 1994, the applicants filed a continuing application from the '826 application. The Patent Office designated this continuing application as application Serial No. 08/257,469 (the "'469 application"). Consistent with the restriction requirement originally issued in the '920 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides in the '469 application. Concurrent with the filing of the '469 application, the applicants then expressly abandoned the '826 application.

59. The Patent Office initially and finally rejected all the claims of the '469 application on prior art and other grounds of patentability in an office action mailed September 12, 1994. The Patent Office provided the applicants until December 12, 1994, with extensions available until March 12, 1995, to submit a substantive response to that office action.

60. Rather than prepare a substantive response to the December 12, 1994 office action, and in order to continue prosecuting claims to an instrument for performing assays for target polynucleotides, on March 8, 1995, the applicants filed a continuing application from the '469

application. The Patent Office designated this continuing application as application Serial No. 08/400,657 (the "'657 application"). Consistent with the restriction requirement originally issued in the '920 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides in the '657 application. Concurrent with the filing of the '657 application, the applicants then expressly abandoned the '469 application.

61. The Patent Office initially and finally rejected all the claims of the '657 application on prior art and other grounds of patentability in an office action mailed April 25, 1995. The Patent Office provided the applicants until July 5, 1995, with extensions available until October 5, 1995, to submit a substantive response to that office action.

62. Rather than prepare a substantive response to the April 25, 1995 office action, on October 25, 1995, the applicants submitted a notice of appeal of the '657 application. Rather than file an appeal brief, and in order to continue prosecuting claims to an instrument for performing assays for target polynucleotides, on March 25, 1996, the applicants filed a continuing application from the '657 application. The Patent Office designated this continuing application as application Serial No. 08/622,491 (the "'491 application"). Consistent with the restriction requirement originally issued in the '920 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides in the '491 application. Concurrent with the filing of the '491 application, the applicants then expressly abandoned the '657 application.

APPLICANTS' EFFORTS TO OVERCOME THEIR INTENTIONAL ABANDONMENT OF THE '505 APPLICATION AND THEIR ALLEGED CLAIMS TO A METHOD OF AMPLIFICATION

63. Gen-Probe is informed and believes, and based thereon alleges, that sometime on or before May 3, 1994, the applicants determined to attempt to reverse their prior intentional abandonment of the alleged invention directed to a method of nucleic acid amplification. As a result of that determination, on May 3, 1994, fifteen months after they failed to respond to the shortened statutory response to the office action of November 5, 1993 and almost eleven months after they further failed to respond to the formal notice of abandonment, applicants attempted to revive their '505 application by filing a formal petition to revive the '505 application. In that

petition, the applicants misrepresented the fact concerning their prior intentional abandonment of the '505 application and claimed that they "unintentionally" failed to respond to the Patent Office. The applicants stated that "[t]he abandonment occurred as a result of the oversight of Applicants representative and was not intended by Applicants."

64. As set forth above, the applicants' claim of unintentional abandonment of the '505 was false. Gen-Probe is informed and believes, and based thereon alleges, that the applicants' failure to respond to the Patent Office's rejection of the claims of '505 application directed to the claimed invention of a method of nuclei acid amplification was intentional. Indeed, the applicants' intentional decision not to respond to the '505 office action was consistent with and driven by applicants' underlying decision to abandon the invention claimed in the '505 application.

65. On October 27, 1994, the Patent Office rendered a decision denying the applicants' petition to revive the '505 application. As the Patent Office explained, the '505 application became abandoned on February 6, 1993, when the applicants failed to respond to the office action of November 5, 1992. Because the petition to revive the '505 application was filed more than one year after the '505 application became abandoned, the petition was barred under 37 C.F.R. 1.137(b). Accordingly, the Patent Office refused to revive the '505 application under 37 C.F.R. 1.137(b).

66. The Patent Office informed the applicants that they might be able to revive the '505 application under the provisions of 37 C.F.R. 1.137(a). However, the Patent Office explained that "in view of the fact that this case has been abandoned for an inordinate period of time, petitioner must show diligence between the time of becoming aware of the abandonment of the above-identified application and the filing of a petition to revive."

67. The applicants declined to seek relief pursuant to 37 C.F.R. 1.137(a), thereby acquiescing to the Patent Office's determination that the '505 patent was abandoned on February 6, 1993.

68. Concurrent with their ultimately unsuccessful effort to revive the '505 application, on May 3, 1994, the applicants filed a new original application that the Patent Office designated as Serial No. 08/238,080 (the "'080 application"), filed. In the '080 application, the applicants did not

initially disclose to the Patent Office that the application was virtually identical to that they intentionally abandoned in the '505 application or of the fact of that abandonment. In addition, the applicants also failed initially to disclose the fact of their concurrent efforts to revive the '505 application. Furthermore, notwithstanding the fact that the applicants knew and intended that the '080 application should be treated as a new original application, applicants did not submit new oaths from the alleged inventors for the '080 application. The applicants also failed to disclose to the Patent Office that, as an original application, the claims of the '080 application were anticipated by the prior publication on August 23, 1989, of the applicants' own European application corresponding to the '920 application, European Application No. 88312135.2.

69. As a result of the applicants' intention to treat the '080 application as an original application and their concurrent failure to submit new oaths to support that application, on June 3, 1994, the Patent Office issued a notice to the applicants by which the Patent Office indicated that it had noted that the applicants had failed to file proper oaths or declarations for the '080 application.

70. In response to the Patent Office's notice to file the missing oaths necessary to support the '080 application, on February July 5, 1994, the applicants submitted a formal response to that notice by which response the applicants first disclosed the prior abandonment of the '505 application and petitioned the Patent Office to consider the '080 application as a continuation application to the '505 application. By that response, the applicants' concurrently petitioned the Patent Office to consider the '080 application as filed under 37 C.F.R. § 1.60 as a continuation of their previously abandoned '505 application. However, through this response and the petition incorporated therein, the applicants continued to misrepresent the prior abandonment of the '505 application and invention as "unintentional."

71. On October 27, 1994, the Patent Office formally dismissed the applicants' petition to revive the '505 application. The applicants did not disclose that decision to the branch of the Patent Office handling the applications' petition in the '080 application to treat the '080 application as a continuation application to the '505 application. In any event, however, on March 14, 1995, the Patent Office formally dismissed that petition as moot and declared that the '080 application would be processed with a filing date of May 3, 1994.

72. The Patent Office decisions denying the applicants' petitions to revive the '505 application and to treat the '080 application as a continuation of the '505 created significant, indeed insurmountable, impediments to the applicants' desire to recant and reverse their earlier abandonment of the '505 application and the alleged invention consisting of the amplification method presented therein. Among other problems raised by those decisions, the applicants knew that unless they could manipulate the priority to which the '080 application was entitled, their own prior publications would constitute statutory bars to patentability.

APPLICANT'S EFFORTS TO FRAUDULENTLY MANUFACTURE CLAIMS OF PRIORITY FOR THE '080 APPLICATION

73. In light of the foregoing fatal impediments to patentability of the method claims presented in the '080 application, the applicants then proceeded to manufacture a scheme to undermine the Patent Office decisions denying their ability to claim priority for the '080 application back through the '505 application. As the first step in that scheme, on December 5, 1995, the applicants submitted a preliminary amendment in the '080 application in which they claimed, for the first time, that the '080 application was a divisional application to the '657 application that the applicants filed on March 8, 1995 to pursue the instrument claims and invention first claimed in the '468 application, as alleged in paragraph 60 of this Amended Complaint.

74. The applicants' efforts regarding and claim of priority of the '080 application to the '657 application were improper for several reasons. First, as indicated above, the applicants had previously elected to pursue only the instrument claims in the '657 application. As such, and without prior disclosure to or permission from the Patent Office, the applicants impermissibly "shift" their method claims back to the claim 24 of the '920 application, and subject to the restriction of July 20, 1990, in that application. As noted hereinabove, the applicants originally filed the chain of applications that included the '657 application in order to prosecute the claims directed to an invention regarding an instrument for performing assays for target polynucleotides, Second, the applicants' efforts to claim that the '080 application was a divisional application of the '657 application was additionally defective because the specification and claims of the '080 patent are different from and not supported by the specification and claims of the '657 application.

75. However, in applicants' zeal to implement their inequitable scheme to overcome the Patent Office determination that the claims of the '080 application were only entitled to claim priority as of May 3, 1994, the applicants overlooked an even more significant defect in their effort to claim priority for the '080 application to the '657 application. Under the patent laws and regulations, an application is only entitled to claim priority to a prior application if such application was co-pending at some point in the "life" of the two applications. Yet, with respect to the applicants' scheme to advance the priority of the '080 application, their claim to priority of the '080 application to the '657 application violated this requirement of co-pendency because the applicants did not file the '657 application until March 8, 1995, nearly one year after the applicants filed the '080 application! The applicants failed to advise the Patent Office of this lack of co-pendency in their December 5, 1995, preliminary amendment. Gen-Probe is informed and believes, and based thereon alleges, that the applicants knew that the representation that the '080 application was a divisional of the '657 application was improper, and that the applicants made this representation with the intent of deceiving and misleading the Patent Office.

APPLICANTS' MISREPRESENTATIONS ABOUT MULLIS, U.S. PATENT NO. 4,683,202.

76. Despite their intentional failure to disclose the fatal defect in their claim of priority in the '080 application, the applicants continued to prosecute the claims of that application. During the course of that continued prosecution of the '080 application, the Patent Office rejected applicants' proposed claims to a method of nucleic acid amplification on the grounds of the disclosure of prior art that included the Mullis patent (U.S. Patent 4,683,202). In response, the applicants argued that the prior art did not teach or disclose purification of a target nucleic acid prior to amplification, yet, that argument was false. Specifically, in their December 5, 1995 Preliminary Amendment, the applicants made the following statements regarding the Mullis patent:

> Applicants submit the Examiner's conclusions is the product of an improper picking and choosing of selective disclosure from the cited references to obtain Applicants' invention and that when the references are considered for all that they teach the references do not disclose or suggest Applicants' invention. For example, while it is true that Mullis (U.S. No. 4,683,202) discloses DNA amplification and some improved sensitivity and ability to isolate

specific nucleoside sequences, Mullis also teaches away from Applicants' invention. Specifically, Mullis teaches:

> The present invention obviates the need for extensive purification of the product from a complicated biological mixture.

(Col. 2, lines 32-34). Mullis reaffirmed this teaching later in the disclosure:

> ***It is not necessary that the sequence to be amplified be present initially in a pure form; it may be a minor fraction of a complex mixture ... or a portion of a nucleic acid sequence due to a particular microorganism which organism might constitute only a very minor fraction of a particular biological sample.***

(***Col. 5, lines 49-56***). Plainly, Mullis teaches that the amplification method of his invention does not include purification before amplification and, in fact, does not require purification. Thus, Mullis teaches away from Applicants' invention.

12/5/95 Preliminary Amendment at p. 16 [emphasis added]. The applicants repeated this representation to the Patent Office regarding the teachings of Mullis in the Amendment filed on October 18, 1996, at pp. 11-12.

77. The paragraph cited by the applicants from the Mullis patent reads in whole:

> Any source of nucleic acid, in ***purified*** or nonpurified form, can be utilized as the starting nucleic acid or acids, provided it contains or is suspected of containing the specific nucleic acid sequence desired. Thus, the process may employ, for example, DNA or RNA, including ***messenger RNA***, which DNA or RNA may be single stranded or double stranded. In addition, a DNA-RNA hybrid which contains one strand of each may be utilized. A mixture of any of these nucleic acids may also be employed, or ***the nucleic acid produced from a previous amplification reaction*** herein using the same or different primers may be so utilized. The specific nucleic acid sequence to be amplified may be only a fraction of a larger molecule or ***can be present initially as a discrete molecule, so that the specific sequence constitutes the entire nucleic acid***. It is not necessary that the sequence to be amplified be present initially in a pure form; it may be a minor fraction of a complex mixture, such as a portion of the .beta.-globin gene contained in whole human DNA or a portion of nucleic acid sequence due to a particular microorganism which

> organism might constitute only a very minor fraction of a particular biological sample. The starting nucleic acid may contain more than one desired specific nucleic acid sequence which may be the same or different. Therefore, the present process is useful not only for producing large amounts of one specific nucleic acid sequence, but also for amplifying simultaneously more than one different specific nucleic acid sequence located on the same or different nucleic acid molecules.

(Col. 5, lines 34-63), emphasis added, underlined is the portion selectively cited by the applicants). Thus, contrary to the applicants' representation to the Patent Office, the omitted portion of the paragraph cited by the applicants expressly teaches that ***purification can and should be used*** with the amplification invention, thereby validating the Examiner's rejection.

78. In addition to the excluded portion of the paragraph of the Mullis patent, the very next paragraph in the Mullis patent states:

> The nucleic acid or acids may be obtained from any source, for example, from plasmids such as pBR322, from cloned DNA or RNA, or from natural DNA or RNA from any source, including bacteria, yeast, viruses, and higher organisms such as plants or animals. ***DNA or RNA may be extracted from blood, tissue material such as chorionic villi or amniotic cells by a variety of techniques such as that described by Maniatis et al., Molecular Cloning A Laboratory Manual (New York: Cold Spring Harbor Laboratory, 1982), pp. 280-281.***

(Col. 5, line 64-col. 6, line 6 [emphasis added]). Maniatis, et al., is a methods manual that teaches a variety of techniques for purifying RNA or DNA from blood, tissue or other cellular material. At pages 197-198 of Maniatis, et al., this reference teaches the purification of mRNA on a solid support using a probe. Thus, the very next paragraph of the Mullis patent following the selective citation by the applicants incorporates a disclosure of ***how*** to purify a sample prior to amplification. Gen-Probe is informed and believes, and based thereon alleges, that the applicants' knowingly and intentionally misrepresented the teachings of the Mullis reference to the United States Patent and Trademark Office. The applicants' selective removal of the first half of the cited paragraph that fully supported the Examiner's rejection based on Mullis and the following paragraph's implicit teaching of how to purify a sample prior to amplification evidence the knowing and intentional nature of the applicants' misrepresentation of the Mullis reference.

APPLICANTS' MISREPRESENTATIONS IN THE REQUEST FOR CERTIFICATE OF CORRECTION FILED FOR THE '338 PATENT

79. On December 14, 1998, the applicants submitted a Request for Certificate of Correction for the '338 patent. Gen-Probe is further informed and believes, and based thereon alleges, that in this Request for Certificate of Correction the applicants represented to the U.S. Patent and Trademark Office that the '505 application was unintentionally abandoned.

80. Gen-Probe is informed and believes, and based thereon alleges, that the applicants made this representation knowing that the true facts were that the '505 application was intentionally abandoned.

81. In the December 14, 1998, Request for Certificate of Correction for the '338 patent, the applicants identified a fatal defect in the claimed priority for the '338 patent involving patent application Serial No. 07/648,468, and patent application Serial No. 07/136,920. By the December 14, 1998, Request for Certificate of Correction, the applicants attempted to cure that fatal defect by, in part, representing to the Patent Office that the applicants did not discover the fatal priority defect prior to the issuance of the '338 patent.

82. The applicants also represented in the Request for Certificate of Correction for the '338 patent that the mistakes for which correction was sought were of minor character, and resulted from errors made in good faith by the applicants.

83. Gen-Probe is informed and believes, and based thereon alleges, that through the aforementioned Certificate of Correction, the applicants knowingly and intentionally misrepresented its knowledge regarding this priority defect with the intent of deceiving the U.S. Patent and Trademark Office. In truth, the applicants were aware of the defect in its claim of priority for the '338 patent well before the issuance of the '338 patent. In addition, Gen-Probe is informed and believes, and based thereon alleges, that the applicants knew that the mistakes for which correction was sought were not of minor character, and did not resulted from errors made in good faith by the applicants, and intentionally misrepresented this to the Patent Office.

84. The applicants further represented in the Request for Certificate of Correction for the '338 patent that the '338 patent was a continuation of the '826 application. However, the '338

patent could not be a continuation of the '826 application, because the disclosure of the '338 patent was not identical to the disclosure of the '826 application.

85. Gen-Probe is informed and believes, and based thereon alleges, that the applicants knew that the '338 patent could not be a continuation of the '826 application, and that through the aforementioned Certificate of Correction, the applicants knowingly and intentionally misrepresented its knowledge with the intent of deceiving the U.S. Patent and Trademark Office.

APPLICANTS' MISREPRESENTATION IN THEIR PETITION UNDER 37 C.F.R. §1.182

86. On December 14, 1998, the applicants filed a petition with the Patent Office under 37 C.F.R. § 1.182 to amend the claimed priority stated in application Serial No. 08/124,826 (the "'826 application") so as to attempt to cure further fatal defects in the priority claim for the '338 patent. At the time of such petition, however, the applicants had previously intentionally abandoned the '826 application.

87. In order to overcome the impediment to its effort to cure the fatal defect in the claim of priority for the '338 patent arising in the '826 application, the applicants argued in its petition to amend the '826 application that an intentionally abandoned application could be amended after abandonment. Gen-Probe is informed and believes, and based thereon alleges, that the applicants misrepresented legal authority to the U.S. Patent and Trademark Office. Gen-Probe is informed and believes, and based thereon alleges, that the applicants' knew that the legal authority it presented to the Patent Office to support its petition to amend the '826 application and cure the otherwise fatal priority defect in the '338 patent did not stand for the proffered proposition and that the applicants knowingly misrepresented this legal authority to the U.S. Patent and Trademark Office with the intent to deceive the Patent Office.

APPLICANTS' FAILURE TO DISCLOSE ALL ART KNOWN TO IT DURING THE PROSECUTION OF THE '338 PATENT

88. During the course of its prosecution of the claims that ultimately issued in the '338 patent, the applicants concurrently presented counterpart patent applications and patent claims to international and foreign patent offices. During the course of the examination and prosecution of those counterpart applications and patent claims, the European Patent Office, for one, identified and

disclosed to the applicants prior art material to the prosecution of the '338 patent claims that was not before or considered by the United States Patent and Trademark Office in the examination of the '338 patent. For example, among this prior art of record in the European Patent Office proceedings but not in the United States Patent Office was the following: EP-A-0200362 (Cetus Corp.); EP-A-0265244 (Amoco Corp.); EP-A-0154505 (Ortho Diagnostic Systems, Inc.); WO-A-8605815 (Genetics Int'l Inc.); WO-A-8701730 (Yale Univ.).

89. Notwithstanding the applicants' duty to disclose all material information to the Patent Office, the applicants failed to disclose the foregoing prior art to the Patent Office. In addition, upon filing the application which led to the issuance of the '338 patent, the applicants did not submit a Form 1449, citing all known material art to the Patent Office, as required to ensure that all known material art is considered by the Patent Office. Gen-Probe is informed and believes, and based thereon alleges, that the applicants knowingly and intentionally failed to submit a Form 1449 and concurrently failed to apprise the Patent Office of prior art identified in the European Patent Office proceedings in order to deceive the Patent Office and prevent it from considering all relevant prior art.

COUNT SIX

UNENFORCEABILITY OF THE '338 PATENT DUE TO LACHES.

90. Gen-Probe repeats, repleads and incorporates herein the allegations of paragraphs 1 through 89 of this complaint.

91. Gen-Probe is informed and believes, and based thereon alleges, that the applicants intentionally, unreasonably, and inexcusably delayed in the prosecution of the invention claimed in the '338 patent, and that Gen-Probe was prejudiced by this delay. Accordingly, the '338 patent is unenforceable against Gen-Probe due to laches.

WHEREFORE, Gen-Probe prays as follows:

1. For declarations:

a. That Gen-Probe's products do not and will not infringe any valid claims of '338 patent;

b. That the claims of the '338 patent are invalid;

c. That the claims of the '338 patent are unenforceable; and

d. Of Gen-Probe's rights and obligations under the License;

2. For a preliminary and permanent injunction enjoining and restraining defendant, its respective officers, agents, servants, employees and attorneys, and all persons acting in concert with them, and each of them:

a. From making any claims to any person or entity that Gen-Probe's products infringe the '338 patent;

b. From interfering with, or threatening to interfere with the manufacture, sale, license, or use of Gen-Probe's products by Gen-Probe, its allied parties, distributors, customers, licensees, successors or assigns, and others; and

c. From instituting or prosecuting any lawsuit or proceeding, placing in issue the right of Gen-Probe, its allied parties, distributors, customers, licensees, successors or assigns, and others to make, use or sell Gen-Probe's products;

3. For recovery of Gen-Probe's damages, as proven at time of trial, and restitution of any sums by which Vysis has been unjustly enriched;

4. For recovery of Gen-Probe's attorneys' fees and costs of suit incurred herein; and

5. For such other and further relief as the Court may deem just and proper.

Dated: March 12, 2001

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99cv2668 H (AJB)
JUDGE MARILYN L. HUFF

MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT

DATE: May 29, 2001
TIME: 10:30 a.m.
DEPT: Courtroom 1

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STATUTES

I. INTRODUCTION

Plaintiff Gen-Probe moves for partial summary judgment under Counts One and Three of its Second Amended Complaint that its nucleic acid test for human immunodeficiency virus ("HIV") and hepatitis C virus ("HCV") does not literally infringe the claims of U.S. Patent No. 5,750,338 ("the '338 Patent")[1]. Gen-Probe's HIV/HCV test is used to screen donated blood using a novel and highly sensitive technology that "amplifies" even a small amount of virus in a sample to a level where it can be detected, using Gen-Probe's own patented method of "Transcription-Mediated Amplification" or "TMA."

Gen-Probe's TMA amplification process uses "primers" that attach to carefully selected portions (or "sequences") of the target organism's nucleic acids. These sequence-specific primers are carefully researched and designed to attach to unique nucleic acids of the target organism, so that the test produces accurate results. The single issue presented by this motion is whether the claims of the '338 patent encompass nucleic acid amplification methods such as TMA, which use sequence-specific primers. By this motion, Gen-Probe shows that the claims of the '338 patent in fact encompass only amplification methods using *non-specific* primers and enzymes. Therefore the claims of the patent do not encompass Gen-Probe's TMA products, and summary judgment should be granted.

As discussed below, the scope of the patent claims is determined primarily from the face of the patent. In this case, the result required by such analysis is confirmed by unequivocal additional evidence. For example, on December 15, 1989, the Director of Business Development and Licensing for Gene-Trak Systems (the predecessor to defendant Vysis, Inc.) clearly described the invention of the '338 patent:

> Cetus, Sibia, Salk, Biotechncia, etc. [e.g., other amplification methods] all claim **specific** primers for amplification, whereas the present invention claims use of the opposite, namely, **non-specific** primers or promoters.

(Exhibit 1 at page 2, emphasis in original).

[1] The '338 Patent is attached as Exhibit 8 to Gen-Probe's accompanying Notice of Lodgment of Exhibits. Unless otherwise specified, all references to exhibits refer to exhibits lodged with such Notice.

Section I of this memorandum sets forth scientific background intended to assist the Court in its analysis of the case. In Section II of the memorandum, Gen-Probe shows that the '338 patent must be construed to cover only non-specific amplification, based on:

1. An analysis of the patent itself, which clearly describes only non-specific amplification methods and states that sequence-specific primers are not necessary when the methods of the patent are used;

2. The expert declaration of Joseph O. Falkinham, III, Ph.D.;

3. Documents and testimony that clearly establish the inventors' and the patents owner's admissions as to scope of the patent claims.

Finally, in section III of the memorandum, Gen-Probe shows that its HIV/HCV test does not literally infringe[2] the claims of the '338 patent, properly construed.

II. SCIENTIFIC BACKGROUND

The '338 patent relates generally to methods for use in nucleic acid diagnostics, including the use of nucleic acid "probes" to detect infectious organisms. In particular, the patent relates to methods by which nucleic acids may be "captured" onto solid supports and copied (or "amplified"), so that small quantities of these nucleic acids may be then detected by probes.

In order to construe the claims of the '338 patent, a very basic familiarity with nucleic acid amplification is required. In particular, it is necessary to understand the distinction between "specific" and "non-specific" primers and enzymes, used in the amplification process to mark the nucleic acid sequences to be copied. A brief overview of the relevant technology is set forth in this section.

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[2] Several inconsequential distinctions arise in this case from the fact that Gen-Probe has licensed the '338 patent. First, because this is a declaratory judgment action brought by Gen-Probe, the plaintiff-defendant positions are reversed from a typical infringement suit. Thus, the patent owner, Vysis, is the defendant. Second, despite the fact that plaintiff Gen-Probe holds a license to the '338 patent and cannot technically be found to "infringe" the '338 patent, the legal issue of infringement is central to Counts One and Three of Gen-Probe's Second Amended Complaint. For example, the terms of the license impose obligations only upon those products of Gen-Probe that would constitute an infringement of the '338 patent but for the license. For the sake of convenience and familiarity, this motion uses the same terminology applicable to a suit for patent infringement.

A. Nucleic Acids

Nucleic acids are molecules that store and transfer genetic information in all living organisms. The two main types of nucleic acids are DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). DNA functions as a stable repository of genetic information, while RNA typically serves to transfer the information stored within DNA to the cell's machinery for making proteins.

DNA and RNA are both composed of chains of chemical sub-units called "nucleotides." Each nucleotide has three components: a sugar ("deoxyribose"), a phosphate group, and a "base" containing nitrogen. There are four types of nucleotides in DNA, each of which has a different base: adenine, thymine, guanine, or cytosine (abbreviated A, T, G, and C). These four "bases" form the building blocks of all DNA[3]. The sugar and phosphate groups within each nucleotide form the backbone of the DNA molecule, linking together the individual nucleotides that make up the molecule. (See Illustration, Exhibit 2).

The "sequence" of the individual A, T, G, and C nucleotides in a DNA molecule encodes the genetic information that instructs the cell how to make particular proteins. Because DNA sequences determine which proteins a cell will make, it is differences in their DNA sequences that make the cells of one organism differ from the cells of another.

DNA in cells ordinarily occurs in a molecular structure in which two "strands" of DNA are specifically bound to one another. Double-stranded DNA is often depicted as a ladder in which each strand forms one side of the ladder and one half of a rung of the ladder. Each nucleotide's base is chemically bonded to a nucleotide base on the opposite strand to form the rungs of the ladder. In its normal state, the ladder is twisted spirally, forming a three-dimensional "double helix" structure. (See Illustration, Exhibit 3).

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[3] RNA also consists of a sequence of four bases comprised of four different nucleotides. The four nucleotides contained in RNA are identical to DNA except that thymine (T) is replaced by uracil (U). Unlike DNA, RNA typically exists as a single strand. However, the nucleotides of RNA have a similar attraction to complementary nucleotides (A binding to U, and C binding to G) and two RNA molecules, or an RNA and a DNA molecule, can form a double helix in which the two strands are joined by complementary base pairing.

In double-stranded DNA, the nucleotides on opposite sides of the ladder are always paired in a precise way. An "A" nucleotide binds only to a "T" nucleotide on the opposite strand, and vice versa. Likewise, a "G" nucleotide binds only to a "C" nucleotide, and vice versa. (See Illustration, Exhibit 4.)

Each combination of an "A" nucleotide with a "T" nucleotide (or a "C" with a "G") is referred to as a "base pair." The way in which each type of nucleotide binds only to one other type of nucleotide is called "complementary base pairing." As a result of complementary base pairing, the sequence of nucleotides on one strand of a DNA molecule necessarily determines the sequence of nucleotides on the opposite strand.

B. Nucleic Acid Probes

The "attraction" of a nucleotide sequence to its "complementary" sequence allows a scientist to use pieces of nucleic acid as "probes" to detect the presence of a target nucleic acid in a test sample. If two complementary pieces of DNA (or RNA) are present in a solution under the right conditions, the complementary bases will come together and bind to form double strands. This method is commonly known as "nucleic acid hybridization." Nucleic acid hybridization techniques can be applied in a diagnostic test to detect an infectious organism (the "target" organism) by the use of a probe that is designed to bind specifically to a nucleic acid sequence that is known to be unique to the target organism. The sample suspected of containing the infectious organism is treated to break open the organism, release its nucleic acids into the solution, and render them single-stranded, if necessary. The specific probe is then added, and conditions conducive to hybridization are established. (See Illustration, Exhibit 5.)

In theory, if the target organism is present in the sample, the "probe" should bind to the target organism's nucleic acids because the sequence of the probe has been designed to be complementary to them. By attaching a detectable "label" to a probe, scientists are able to determine how much, if any, probe has bound to sequences from the target organism.

Nucleic acid probes are generally designed based on the fact that each species of organism has its own unique genome. By the early 1980's, scientists were routinely determining the specific nucleotide sequences of different species' DNA and RNA and searching for sequences that were

common to and different among various organisms. Using this information, scientists could design probes that, under the right conditions, would bind to nucleic acid sequences characteristic of a specific target organism and not to sequences of other organisms.

However, related species have substantial portions of their DNA that are identical. Generally, more closely related species have more DNA sequences in common. DNA sequences that are common to a target organism and other organisms can interfere with the specific detection of the desired target. For example, the sequence CGTAG shown in the Illustration of Exhibit 2 might appear in the DNA of many species. A probe that is complementary to this sequence would bind to the DNA of the target organism, and also to the DNA of other species that contain the same sequence. Samples that did not contain the target organism, but did contain one or more of the other species, would be falsely analyzed if such a probe were to be used in a diagnostic test.

Thus, it is desirable to have a probe that binds only to DNA of the target pathogen and not to DNA contained in other organisms. A probe that consists of a DNA sequence unique to the target organism and which therefore binds exclusively to the DNA of the target organism, and not to DNA of other organisms, is said to be "specific" for the target organism.

C. Target Capture

Target capture techniques are used in nucleic acid methods to isolate a particular nucleic acid of interest prior to detection or other steps. In target capture methods, the target nucleic acid is bound to a solid support, such as a filter, particle, or a bead, which allows the target to be removed from the sample in which it was originally contained. The immobilized target nucleic acid is directly detected with a probe, amplified prior to detection, or used for other purposes.

The target nucleic acid can be immobilized on the solid support either by direct attachment or by the use of an intermediate "capture probe." A capture probe is a nucleic acid sequence that is designed to bind with the target organism's DNA or RNA and also attach to the solid support (See Illustration, Exhibit 6).

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D. Amplification

Often, it is necessary to detect very small numbers of infectious organisms in a sample. This is particularly true when screening for the presence of the organism in the absence of a full-blown infection. Examples include screening blood intended for transfusion for the presence of viruses such as HIV. In these situations, the presence of even small numbers of organisms may lead to the transmission of infection from one individual to another.

Scientists have long understood that detection of a small number of organisms in a sample requires that the number of "target" organisms be increased in number in order to achieve a detectable level. There are many ways to accomplish this. For example, one classic way to detect low numbers of organisms is to transfer the sample to culture media that will support the growth of the organism. After a suitable time, the number of organisms will generally have increased sufficiently to allow them to be detected directly by hybridization or other methods.

A faster approach is to increase the target organism's nucleic acid through processes known as "nucleic acid amplification." Amplification procedures are generally performed with enzymes and primers. Enzymes are protein molecules that catalyze biological reactions. "Polymerase" enzymes are used to copy a DNA or RNA strand to make its complement. Such naturally occurring enzymes are normally used in cellular processes to make copies of the organism's genes to be passed on to its progeny.

Scientists have learned to use enzymes such as polymerase to increase the amount of a DNA or RNA in a sample up to a billion-fold. By making copies of the target organism's nucleic acids, the amount of target that is available to bind with a probe in a detection step is increased to easily detected levels. One of the most famous amplification techniques is the "polymerase chain reaction" (PCR), which uses DNA polymerase and specific primers to multiply specific nucleotide sequences within a nucleic acid. Dr. Kary Mullis received the Nobel Prize in chemistry for his 1983 invention of PCR.

"Primers" are short pieces of DNA that are used in amplification methods to cause an enzyme such as DNA polymerase to start its copying action at a certain point along a nucleic acid sequence. Like probes in the detection step, primers work by binding (hybridizing) to a

complementary nucleotide sequence in the target nucleic acid. DNA polymerase then copies the target nucleic acid beginning at the point where the primer attached. (See Illustration, Exhibit 7.) The procedure can be repeated many times, resulting in copies of the copies. This process of "geometric" or "exponential" amplification produces millions of copies of the target segment that is bounded by the sites where the primers attached.

Primers used in amplification processes can be either specific or non-specific. "Specific" primers are carefully designed to bind only to a pre-selected nucleic acid sequence of a particular target organism, usually a sequence selected to be unique to that organism. Non-specific or "random" primers can be used with DNA polymerases to copy random portions of the nucleic acid sequence of the target organism. When random primers are used, the resulting amplification process is referred to as "non-specific" because DNA synthesis begins at random locations all over the target nucleic acid and any other nucleic acids that may be present in the sample are also amplified. Using random, non-specific primers avoids the work required to select, make, and test specific primers for each individual target organism.

Another form of enzymatic amplification makes copies of RNA from a DNA sequence using an enzyme called "transcriptase." Transcriptases are types of polymerase that make an RNA sequence that is complementary to an initial DNA sequence. The process of making this RNA copy ("transcription") may also be specific or non-specific. Transcriptases do not use primers but instead begin RNA synthesis at special DNA sequences ("promoter sequences"). Many transcriptases only carry out specific transcription in the presence of other special protein factors (often called "subunits"). In the absence of these subunits, the "core" transcriptase enzyme binds randomly to the DNA and starts making RNA molecules at multiple random sites.

III. THE CLAIMS OF THE '338 PATENT MUST BE LIMITED TO NON-SPECIFIC AMPLIFICATION METHODS

By this motion, Gen-Probe moves for summary judgment on the issue of literal infringement inherent in Counts One and Three of the Second Amended Complaint. A determination of the issue of infringement involves a two-step analysis. First, the Court must construe the claims at issue in order to determine their meaning and scope. Second, the Court

must determine whether the claims, as properly construed, encompass the technology used by Gen-Probe. *WMS Gaming Inc. v. International Game Technology*, 184 F.3d 1339, 1346 (Fed. Cir. 1999); *Zelinski v. Brunswick Corp.*, 185 F.3d 1311, 1315 (Fed. Cir. 1999). The first step of the Court's analysis, construction of the claims, often decides the question of infringement. *Netword LLC v. Centraal Corp.*, 242 F.3d 1347, 1350 (Fed. Cir. 2001).

Claim construction, the judicial statement of what is and is not covered by the technical terms and other words of the claims, is a question of law to be decided by the Court alone. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). The focus of the Court's inquiry in claim construction is on the objective test of what one of ordinary skill in the art would have understood the terms used in the patent claims to mean, as of the date the patent application was filed.[4] *Id* at 985-86.

In determining the proper construction of a claim, the Court has numerous sources that it may properly utilize for guidance. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). These sources include both "intrinsic" evidence (*e.g.*, the patent specification) and "extrinsic" evidence (*e.g.*, expert testimony and the inventor's/patent owner's own descriptions of the invention). *Id.*

The starting point for any claim construction is the patent claim itself. *Pitney Bowes, Inc. v. Hewlett Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). However, "claims are always construed in light of the specification, of which they are a part." *Netword*, 242 F.3d at 1352. "The claims are directed to the invention that is described in the specification; they do not have meaning removed from the context in which they arose." *Id.* at 1352; *Slimfold Mfg. Co. v. Kinkead Indus., Inc*, 810 F.2d 1113, 1116 (Fed. Cir. 1987) (claims are not interpreted "in a vacuum," but are read and understood in light of the specification of which they are a part).

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[4] Gen-Probe submits that, for the purposes of this motion at least, any disagreement or dispute as to the actual level and sophistication of the "person or ordinary skill" in 1987 is insubstantial at best. As of 1987, all of the inventors held doctorate degrees in molecular biology or equivalent technical disciplines. For the purpose of this motion, Gen-Probe will submit to that level of skill as "ordinary" for the Court's purposes.

Thus, when a word or phrase in a claim is used in the specification, the relevant passages must be considered in order to determine what the term means in the claim. *Renishaw PLC v. Marposs Societa' Per Azioni*, 158 F.3d 1243, 1248 (Fed. Cir. 1998). It is *always* necessary to review the patent specification as part of the claim construction process. *United States v. Adams*, 383 U.S. 39, 49 (1966) (claims are to be construed in light of the specifications and both are to be read with a view to ascertaining the invention); *Vitronics Corp.*, 90 F.3d at 1582; *Markman*, 52 F.3d at 979-80.

Ideally, the meaning of a term to one of ordinary skill in the art can be determined from the face of the patent, *e.g.*, the intrinsic evidence. *Markman*, 52 F.3d at 979-80. While the Court's primary focus is on the patent specification, reliable extrinsic evidence may also be considered:

> [I]t is entirely appropriate, perhaps even preferable, for a court to consult trustworthy extrinsic evidence to ensure that the claim construction it is tending to form from the patent file is not inconsistent with clearly expressed, plainly apposite, and widely held understandings in the pertinent technical field.

Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1309, (Fed. Cir. 1999). In *Pitney Bowes*, Judge Michel further pointed out:

> While a judge is well-equipped to interpret the legal aspects of the document, he or she must also interpret the technical aspects of the document, and indeed its overall meaning, *from the vantage point of one skilled in the art.* ... Although the patent file may often be sufficient to permit the judge to interpret the technical aspects of the patent properly, *consultation of extrinsic evidence is particularly appropriate to ensure that his or her understanding of the technical aspects of the patent is not entirely at variance with the understanding of one skilled in the art.*

Id., citing Mantech Envtl. Corp. v. Hudson Envtl. Servs., Inc., 152 F.3d 1368, 1373 (Fed. Civ. 1998) (emphasis added). These principles guide the construction of the claims of the '338 patent[5].

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[5] Gen-Probe's motion for summary judgment is based solely on the claim construction arguments expressly set forth in this memorandum. Gen-Probe believes that the claims of the '338 patent must also be limited to non-specific amplification on the basis of 35 U.S.C. § 112, paragraph six (means-plus-function, step-plus-function). Gen-Probe reserves its arguments with respect to claim construction pursuant to 35 U.S.C. § 112, paragraph six. Furthermore, Gen-Probe believes that the parties dispute still other terms of the '338 patent that are not germane to the Court's resolution of this motion.

A. The Claims of the '338 Patent

The '338 patent, Exhibit 8, consists of the specification, including drawings, and the claims. The '338 patent contains six independent claims (claims 1, 7, 19, 27, 28 and 34). Each of these claims is generally directed to a method of, or a kit for, amplifying and/or detecting a target polynucleotide (i.e., a nucleic acid), wherein the target is first isolated on a support.

Each of the claims contains a step of "amplifying" the target polynucleotide or sample. For example, claim 1 provides:

> 1. A method for amplifying a target polynucleotide contained in a sample comprising the steps of:
>
> (a) contacting the sample with a first support which binds to the target polynucleotide;
>
> (b) substantially separating the support and bound target polynucleotide from the sample; and
>
> (c) *amplifying* the target polynucleotide.

(Exhibit 8 at col. 32, ll. 27 to 33, emphasis added.) This motion concerns the proper construction of the term "amplifying" as used in the claims of the '338 patent.

B. The Teaching of the Patent

The issue of what a skilled scientist would have understood the term "amplifying" to mean is determined primarily from the specification of the patent. *Netword,* 242 F.3d at 2; *Markman*, 52 F.3d at 979-80.

In the "Background of the Invention" section, the patent defines the term "amplify" in very broad terms that encompass many different methods of amplification, including many that were already well known in the prior art. Throughout the remainder of the specification, however, the inventors teach only *non-specific* amplification because a suggested benefit of the invention is that it *eliminates* the need to design and prepare specific primers and/or the need to use specific enzymes.

Significantly, the specification sets forth four examples (Examples 4 through 7) of the amplification methods taught by the inventors. Immediately before the first example that includes an amplification step (Example 4), the inventors expressly set forth their teachings with respect to

amplification methods. Referring to the target capture methods described in Examples 1 through 3, the inventors stated:

> The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by ***nonspecific*** *replication using standard enzymes* (polymerases and/or transcriptases).

('338 patent, Exh. 8, at col. 30, ll. 14-18, emphasis added.)

The inventors then made clear that the reference to non-specific amplification methods was intentional and pointed out that one of the express benefits of their invention was that it permitted the use of non-specific enzymes and non-specific primers:

> Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ **non-specific** enzymes or primers. **Thus no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of targets.**

(*Id.* at col. 30, ll. 30-40, emphasis added.) This teaching clearly expresses that a primary benefit of the invention is the ability to use non-specific enzymes or primers, thereby avoiding the need to craft specific primers for each particular target organism and the need to use other individualized reagents such as specific transcriptases.

C. The Examples of the Patent

Immediately following the fundamental teaching of the '338 patent as set forth above, the specification sets forth four examples of the amplification methods contemplated by the inventors ('338 Patent, Exh. 8, col. 30, l. 43 to col. 32, l. 25, examples 4-7). Consistent with the teaching of the patent that sequence-specific primers and specific enzymes are not necessary, each example suggests and describes amplification methods that use only non-specific primers and enzymes.

Example 4 illustrates "the use of RNA polymerase to amplify target DNA." ('338 Patent, Exh. 8, at col. 30, ll. 44-45.) It describes a method for amplifying the capture DNA by non-specific amplification using polymerases that lack transcriptional specificity. (*Id.* at col. 30, l. 59 - col. 31, l.17). Example 4 discloses only non-specific amplification:

> Q. So recapping the examples, examples one through three disclose capture methods without amplification?

A. Yes.

Q. And example four discloses linear *nonspecific* amplification?

A. Yes.

(Lawrie Depo., Exh. 9, at 231:7-13, emphasis added.)

Example 5 also describes a non-specific amplification method in which that the target DNA is replicated using random (*i.e.*, non-specific) primers and non-specific transcription of that DNA into RNA:

> In this example, both non-specific replication of target DNA and transcription of that DNA are used to amplify capture target DNA.... Because the primers are *random*, some will, simple (sic) as a matter of statistics, bind to and cause replication of sample sequences, no matter what those sequences are. . . .

('338 Patent, Exh. 8, at col. 31, ll. 24-54, emphasis added.) Example 5 discloses only non-specific amplification. (Lawrie Depo., Exh. 9, at 231:14-16; Richards Depo., Exh. 10., at 139:23 – 140:3.)

Example 6 describes replication of target DNA using DNA polymerase and *random* hexamer[6] oligonucleotides "to bring about *non-specific* double-stranded DNA synthesis" ('338 Patent, Exh. 8, at col. 31, ll. 63-64), using a series of repeated heat denaturation and enzyme replacement steps (*id.*, col. 31, l. 64 to col. 32, l. 19). Example 6 also discloses only *nonspecific* amplification. (Lawrie Depo., Exh. 9, at 231:17-19; Richards Depo., Exh. 10, at 140:9-13.)

Finally, Example 7 describes *non-specific* amplification using an RNA polymerase, Qß replicase:

> In this example, rRNA and RNA transcribed from target DNA is purified using a capture probe, described above. The hybrid duplex is then denatured and single stranded nucleic acids are then replicated *non-specifically* using Qß replicase...

('338 Patent, Exh. 8, at col. 32, l. 10-19.) Example 7 discloses only nonspecific amplification. (Lawrie Depo., Exh. 9, at 231:20–22; Richards Depo., Exh. 10, at 141: 3-7.)

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[6] Certain of the examples and drawings refer to "hexamer" primers. Hexamer primers are generally understood to mean random (*e.g.*, non-specific primers) used in non-specific amplification methods. (Richards Depo., Exh. 10, at 77:19 - 78:3; 133:2-9; 133:19-22.)

D. The Drawings of the Patent

The first pages of the '338 patent provide drawings of various methods encompassed by the invention. Any drawings included in the patent are a proper reference for determining claim meaning. *Wright Medical Technology, Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1443 (Fed.Cir.1997) ("The proper construction of the claims is based upon the claim language, the written description portion of the specification including any relevant drawings. . . ."); *Raleigh v. Tandy Corp.*, 1997 WL 26299, *3 (N.D. Calif. Jan. 10, 1997) (interpreting "supporting means" as requiring a flat structure; "the supporting platform ... is pictured flat in the figures depicting all embodiments of the invention").

The first 3 drawings (Figure 1a to Figure 3) depict target capture methods alone, without amplification. Figures 4, 5 and 6 depict target capture followed by amplification using only non-specific primers or enzymes. The drawings included in the patent are discussed and described in the text of the patent specification ('338 Patent, Exh. 8, at cols. 10 - 19.) The text of the specification expressly states that in each of the drawings that include amplification (*id.*, Figures 4, 5 and 6) "the isolated target is *non-specifically* amplified to form a multitude of amplification products." (*Id.* at col. 15, ll. 56-58, emphasis added.)

E. As Used in the Claims of the '338 Patent, "Amplifying" Means Amplification with Non-Specific Primers or Enzymes

Reading the teaching, examples, and drawings included in the '338 patent specification, one of ordinary skill in the art could only conclude that the term "amplifying" as used in the claims means amplification methods using non-specific primers or enzymes as disclosed and taught in the patent. The patent expressly teaches that sequence-specific primers are not necessary. Therefore, a person of ordinary skill in the art would not understand the term "amplifying" as used in the claims to encompass amplification using specific primers. Similarly, based on the explicit teaching that standard, non-specific enzymes are not necessary, the ordinarily skilled practitioner of the art would not understand the term "amplifying" to encompass amplification using specific transcriptases and promoter sequences. The invention of the '338 patent cannot encompass methods that the specification states become unnecessary due to the

benefits of a target capture step prior to amplification. *See Evans Medical Ltd. v. American Cyanamid Co.*, 11 F. Supp. 2d 338, 355-56 (S.D.N.Y. 1998), *aff'd without op.*, 215 F.3d 1347 (Fed. Cir. 1999) ("There would be no quid pro quo for granting a patentee the right to exclude others from using something that his specification clearly instructs them *not* to use.").

Numerous Federal Circuit decisions demonstrate that the claims of the '338 Patent must be limited to amplification methods using non-specific primers or enzymes. Although the specification of a patent need not present every embodiment of the invention and the claims are not limited to the preferred embodiment of the invention, neither do the claims enlarge what is patented beyond what the inventor has described as the invention.

For example, in *Wang Laboratories, Inc. v. America Online, Inc.*, 197 F.3d 1377 (Fed. Cir. 1999), the patent specification described and taught only one embodiment of an invention, and the Federal Circuit held that the claims of the patent were correctly limited to that one embodiment. *Id.* at 1383. *Wang Labs* involved patent claims directed to an online information system. The accused infringer filed a motion for summary judgment of non-infringement. The outcome of the motion depended upon construction of the term "frame" as used in the patent claims. The parties agreed that the term "frame" could, in general usage, be applied to both "bit-mapped" and "character-based" displays and the specification referred generally to both types of frames. However, the examples in the patent specification described and taught character-based displays only. The district court therefore construed the term "frame" to be limited to the type of frame disclosed and described in the specification in such a manner as to constitute the invention of the patent. On appeal, the Federal Circuit affirmed.

In reaching its conclusion that the term "frame" was properly construed to be limited to the character-based displays expressly described in the specification, the Federal Circuit first found that the only systems actually described and enabled in the specification were character-based displays:

> The only system that is described and enabled in the '669 specification and drawings uses a character-based protocol. The specification mentions non-character-based protocols, for example, *in the "Background of the Invention" statement* . . . The district court viewed the references to bit-mapped protocols *as*

> *acknowledgments of the state of the art, and not as an enlargement of the invention described in the patent.* We agree, and conclude that the references to other known protocols do not describe them as included in the applicant's invention, and that the specification would not be so understood by a person skilled in the field of that invention.

Id. at 1382 (emphasis added).

The Federal Circuit then held that claims could not be interpreted to have a meaning or scope that would lead to their invalidity:

> Wang argues that it is irrelevant to the construction of the claims whether the specification contains an enabling description of any bit-mapped decoder, stating that enablement is a requirement for validity, not a factor in claim construction. However, the claims are not properly construed to have a meaning or scope that would lead to their invalidity for failure to satisfy the requirements of patentability.

Id. at 1382-83. The court next held that the requirements of 35 U.S.C. § 112 (written description and enablement[7]) would not be met with respect to protocols other than character-based frames:

> Although Wang is correct that a claim is not invalid simply because it embraces subject matter that is not specifically illustrated, in order to be covered by the claims that subject matter must be sufficiently described as the applicant's invention to meet the requirements of section 112. This requirement was not met as to protocols other than character-based.

Id. at 1383.

The Federal Circuit then rejected the patentee's argument that character-based protocols were simply a preferred embodiment:

> Wang states that the character-based protocol is simply a preferred embodiment and that the embodiment described in the specification does not set the boundaries of the claims citing *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1186, 48 USPQ2d 1117, 1124 (Fed. Cir. 1998), for its statement that limitations from the specification are not to be read into the claims. AOL and Netscape respond that when the subject matter that is claimed is the only subject matter that is described and enabled in the specification, that is the invention itself, and not simply a "preferred" example of a broader invention that is not described and enabled.... Whether an invention is fairly claimed more broadly than the "preferred embodiment" in the specification is a question

[7] 35 U.S.C. § 112 provides in pertinent part: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

> specific to the content of the specification, the context in which the embodiment is described, the prosecution history, and if appropriate the prior art, for claims should be construed, when feasible, to sustain their validity. The usage "preferred" does not of itself broaden the claims beyond their support in the specification.... *The only embodiment described in the '669 patent specification is the character-based protocol, and the claims were correctly interpreted as limited thereto.*

Id. at 1382 (empahsis added), *citing Modine Manufacturing Co. v. United States International Trade Commission*, 75 F.3d 1545, 1551 (Fed. Cir. 1996), the court explained that "when the 'preferred embodiment' is described as the invention itself, the claims are not entitled to a broader scope than that embodiment." 197 F.3d at 1383.

Wang Labs is directly analogous to the facts in this case. Both cases involve a summary judgment motion of non-infringement. Both cases involve a claim term that could be construed narrowly based on the patent specification or more broadly based on general usage. In *Wang Labs*, the claim term "frame" had a meaning in general usage that encompassed both bit-mapped and character-based protocols and the "Background of the Invention" section contained references to support that meaning. In this case, too, the term "amplifying" has a meaning in general usage that might encompass both specific and non-specific amplification.

Both *Wang Labs* and the instant case involve specifications that describe and teach only one aspect or embodiment of the claim term at issue. In *Wang Labs*, the specification described and taught only character-based display frames. While there were references in the specification to other types of frames, the court found that these were not described in such a way as to be included in the applicant's invention. Similarly, in the instant case, the specification describes and teaches only non-specific amplification. Indeed, the specification states that the ability to use non-specific primers and enzymes is a primary benefit of the '338 invention. Here, too, as in *Wang Labs*, the patent obviously does not "enable" an invention that it does not describe, and the claims should not be construed in such as manner as to render them invalid for lack of enablement. Thus, the holding in *Wang Labs* is particularly applicable to this motion for summary judgment, and the term "amplifying" as used in the claims of the '338 patent must be limited to non-specific amplification with the primers or enzymes described in the '338 specification. Any other result

would mean that the claims cover methods of amplification using specific primers or enzymes that are not described nor taught in the '338 Patent and which the patent says can be avoided.

In *SciMed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337 (Fed. Cir. 2001), the Federal Circuit also held that a claim term was to be construed to be limited in accordance with the specific embodiments disclosed in the specification. The Federal Circuit held in *SciMed Life* that the term "lumens" in certain patent claims, although not limited by the claims themselves, was required to be construed to encompass only *coaxial* lumens, and not to encompass "dual" or "adjacent" lumen configurations. The court based its ruling on the fact that all embodiments in the patent specification were limited to coaxial lumens, and that the specification highlighted that one of the advantages of the invention was the use of the coaxial lumens. *Id.* at 1342-43. Likewise, in the instant case, all of the examples in the '338 patent specification involving amplification are limited to non-specific amplification, and the specification highlights the advantage obtained because the need for specific primers and enzymes may be avoided. Therefore, just as in *SciMed*, the '338 Patent's claims must be limited to non-specific amplification.

This conclusion is also supported by *O.I. Corp. v. Tekmar Co.*, 115 F.3d 1576 (Fed. Cir. 1997). *O.I. Corp.* involved the meaning of the word "passage" in a claim. The court held that the term "passage" was limited to non-smooth or conical types of passages because the only passage structures contemplated by the specification were non-smooth or conical:

> All of the "passage" structures contemplated by the written description are thus either non-smooth or conical. In addition, the description expressly distinguishes over prior art passages by stating that those passages are generally smooth-walled. OI has not identified anything in the prosecution history contrary to those statements. Therefore, we conclude that one skilled in the art reading the claims, description, and prosecution history would conclude that the term "passage" in claim 17 does not encompass a smooth-walled, completely cylindrical structure.

Id. at 1581.

The facts of *O.I.* are analogous to the instant case. In *O.I.*, while the claim contained the general term "passages," the specification described only non-smooth or conical passages. Likewise, while the '338 Patent claims contain the general term "amplifying," the specification

describes only non-specific amplification methods and states that specially tailored primers and specific enzymes are not necessary when the invention is used.

The case of *Kraft Foods, Inc. v. International Trading Co.*, 203 F.3d 1362 (Fed. Cir. 2000) is also directly applicable to the instant case. The Federal Circuit found that the term "protecting back panel" was properly construed as limited to a "relatively stiff" panel because that was the only type of back panel described in the specification. 203 F.3d at 1367-69. The court reached this conclusion despite the fact that other claims did not expressly contained a "relatively stiff" limitation:

> Notwithstanding Kraft's contentions, we agree with the district court that the written description and prosecution history overcome any presumption arising from the doctrine of claim differentiation, and thus approve the district court's construction of claim 2's protecting back panel as one that must be relatively stiff. . . . With respect to the written description, every disclosed embodiment that employs a back panel employs one that is relatively stiff. . . .

Id. at 1368. Thus, *Kraft* provides additional support for the conclusion that the term "amplifying" in the '338 Patent claims must be construed as meaning non-specific amplification.

Other decisions have similarly determined that claims terms must be determined to be consistent in scope with the disclosures of the specification. *See, e.g., Netword*, 242 F.3d at 1353 (district court correctly construed "local server computer" to mean a local server computer that has a limited database of aliases and that may request updates from a central registry computer); *Toro Co. v. White Consolidated Industries, Inc.*, 199 F.3d 1295, 1301-02 (Fed. Cir. 1999) ("cover" interpreted to encompass only permanently attached covers because specification disclosed only attached covers and described advantages of unitary structure as important to the invention); *Biogen, Inc. v. Berlex Labs, Inc.*, 113 F. Supp. 2d 77, 98 (D.Mass. 2000) ("cell incorporating a DNA construct" limited to a cell containing the particular DNA construct specifically described in the specification).

The analysis in these cases is directly applicable to the claim construction issue presented here. At numerous points, the '338 specification describes the claimed invention only in terms of using non-specific primers or enzymes and states that this characteristic is an advantage of the invention. Read together, these portions of the specification lead to the inescapable conclusion

that "amplifying" would have been understood by one skilled in the art at the time the patent application was filed to mean non-specific amplification using non-specific primers or enzymes.

F. Extrinsic Evidence Confirms the Claim Construction

In addition to the ample intrinsic evidence presented in the specification to show that the investors intended to limit their invention to non-specific amplification techniques and that intention is apparent to one of ordinary skill, ample extrinsic evidence exists to confirm that intention and interpretation. One of the sources of information that the Court may properly consider in claim construction is the declaration of an expert witness. Rule 702, Fed. R. Evid.; *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 589 (1993); *Pitney Bowes*, 182 F.3d at 1308-09 (Fed. Cir. 1999) (consultation of extrinsic evidence appropriate to ensure that claim construction is not entirely at variance with the understanding of one skilled in the art). Gen-Probe has submitted the declaration of Joseph O. Falkinham III, Ph.D., which confirms what is apparent from the face of the patent: One of ordinary skill in the art would have understood the term "amplifying" in the '338 patent to include only the non-specific amplification methods taught by the patent. One of ordinary skill in the art would not have understood the term "amplifying" to include other amplification methods that use sequence-specific primers or enzymes.

Testimony from one of the inventors and from other witnesses confirms this conclusion. In 1983 Dr. Kary Mullis invented a form of specific amplification using sequence-specific primers, called the "polymerase chain reaction." Dr. Mullis received the Nobel Prize in chemistry for his invention. If the inventors had intended to suggest and claim the combination of target capture with specific primer methods of amplification such as PCR, it would have been easy for them to do so.

The PCR method was first described at a scientific meeting in the summer of 1985 and was published in December 20, 1985. Saiki et al., "Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia," SCIENCE 230:1350-54 (1985). Within the scientific community, PCR was immediately "big news." (Richards Depo, Exh. 10, at 38:6-8.) Although the application leading to the '338 patent was filed two years after the disclosure of PCR, the patent does not disclose or teach the combination of target capture with

amplification methods using specific primers, such as PCR.

While the '338 inventors could have included an example that showed the combination of target capture and sequence-specific amplification (such as PCR), they instead described in the specification a method that permitted scientists to *avoid* the use of sequence-specific primers. That is, the inventors chose to describe their invention as an *alternative* to specific primer methods such as PCR. This conclusion, which is inescapable from reading the specification, is supported by testimony from the inventors concerning the nature of their invention. Inventor Jon Lawrie testified that the patent was meant to cover *new* amplification methods using non-specific primers, not already-known methods such as PCR:

> Q. Can you recall any reason that a reference to PCR might have been intentionally omitted from the patent application?
>
> A. Yes....
>
> Q. If there's no reference in the ['338] patent to combining target capture with PCR, do you have any explanation as to why it is not there?
>
> A. I believe that it was a separate, the thought behind this [referring to the '338 patent] was coming up with *new* methods of amplification, not old ones.
>
> Q. For the purposes of what you just said you classify PCR as an old method of amplification?
>
> A. PCR itself was described in the patent, issued patent [e.g., it was an "old" method].
>
> Q. And your understanding of the 338 patent was that it was directed to other methods of amplification?
>
> A. The, it was, it was directed to the methods disclosed by, you know, *the methods separate from PCR.*
>
> Q. Those being the methods, for example, as the methods set forth in example six and seven?
>
> A. Yes.

(Lawrie Depo., Exh. 9, at 178:19 - 180:11.)

> Q. However, your recollection of why - of if there's no - your explanation of why there might not be a reference to PCR in the patent is that the patent wasn't intended to cover old methods of amplification such as PCR; is that right?

A. The patent was intended to cover the discoveries by myself, Halbert and King that there should be in some, you know, disclosure back at Amoco. That's what the patent was about. Why PCR was left out I can just speculate. It wasn't what we came [up] with, it was in the previous, it was a previous older method.

Q. You were looking for other things?

A. Yeah.

(*Id.* at 180:23 – 181:13.)

Dr. Lawrie's testimony explains why the inventors of the '338 patent described and taught only amplification with non-specific primers or enzymes. They considered that particular combination to *be* their invention. They believed that once "specificity" was added to the overall process by the use of capture probes, it was not necessary to use specific primers or enzymes in the amplification step. The combination of specific target capture and *non-specific* amplification was what the inventors believed they had invented, that is what the '338 patent teaches, and that is all the claims of the '338 patent -- properly construed -- encompass.

Although the Federal Circuit has routinely cautioned District Courts not to rely upon self-serving inventor testimony to *expand* the scope and construction of patent claims, the Court and other District Courts have recognized the significant evidentiary and persuasive value of extrinsic evidence provided by admissions by inventors and patent owners that confirm the limited scope of patent claims. For example, in *Jonsson v. Stanley Works*, 903 F.2d 812 (Fed. Cir. 1990), the Federal Circuit affirmed a district court's order narrowly construing patent claims consistent with the admissions against interest of the inventor. *Id.* at 818. Dr. Lawrie's testimony satisfies the well-settled view of relevance in this instance. *See Components, Inc. v. Western Electric, Co.*, 52 F.R.D. 379, 382 (D. Me. 1971); *Canadian Ingersoll-Rand Co., Ltd. v. Peterson Products of San Mateo, Inc.*, 350 F.2d 18, 24 (9th Cir. 1965).

Other evidence reinforces Dr. Lawrie's testimony. On December 15, 1989, Dr. James C. Richards, the Director of Business Development and Licensing for Gene-Trak Systems, admitted that the '338 patent encompassed only amplification with non-specific primers and explicitly contrasted the methods of the patent with other methods of amplification using specific primers.

Dr. Richards' analysis was set forth in a letter to one of Gene-Trak's partners, Amoco Technology Company. (See Exhibit 1)

Dr. Richards first discussed the fact that the pending patent application encompassed the use of random, non-specific primers. He then discussed the effect of combining non-specific amplification with the use of an initial target capture step. Finally, he pointedly contrasted the invented method with other known methods that used specific primers or promoters (*e.g.*, enzymes):

> Cetus, Sibia/Salk, Biotechnica, etc. all claim **specific** primers for amplification whereas the present invention claims uses of the opposite, namely, **non-specific** primer or promoters.... Following extensive washing, captured target polynucleotides could be released and the non-specific amplification process could take place.

(Exhibit 1 at page 2, emphasis in original).

At the time he wrote this letter, Dr. Richards held a Ph.D. in Microbiology and Biochemistry from Southern Illinois University. (Richards Depo., Exh. 10, at 7:17-20.) He had worked at Amoco from February 1984 to October 1986, when he moved to Gene-Trak. (*Id.* at 28:1 - 29:2-4.) At Amoco, Dr. Richards worked with the four inventors of the '338 patent, and Dr. Lawrie had explained to him the nature of the invention that is the subject of the patent. (*Id.* at 30:5-11; 35:13 – 36:16.)

From October 1986 to December 1989 when he wrote the letter, Dr. Richards worked at Gene-Trak[8] with the four inventors. (*Id.* at 29:2-4; 41:10-12.) As Gene-Trak's Director of Business Development and Licensing, Dr. Richards managed the company's technology assets and technology needs. (*Id.* at 44:18 – 45:9.) As part of his job, Dr. Richards evaluated numerous technologies and participated in licensing negotiations. (*Id.* at 47:22 – 48:24.)

When presentations on patent matters, including target capture patents, were made to the Gene-Trak partnership committee and to the Gene-Trak scientific advisory board, Dr. Richards made those presentations. (*Id.* at 60:8-13; 82:3-6; 150:9-14; 151:1-4.) Dr. Richards was a member of the Gene-Trak patent committee and discussed patents with Gene-Trak's patent counsel. (*Id.* at

[8] Gene-Trak was a partnership formed by Amoco and Integrated Genetics in the summer of 1986. Gene-Trak Systems became Vysis in 1991.

150:15-21.)

When Dr. Richards wrote his December 1989 letter, his sources of knowledge about the application for the '338 patent were discussions he had held about the patent application with Tony Janiuk, Gene-Trak's patent counsel, and with inventor Dr. Jon Lawrie. (*Id.* at 152:5-13; 186:11-21.) In his December 1989 letter to senior management, Dr. Richards tried to be as accurate as possible, and he has never since concluded that the way he described the invention was inaccurate. (*Id.* at 154:9 - 156:12; 164:17-22; 165:14-19.) Dr. Richards' letter makes clear that the invention of the '338 patent was the use of target capture *with non-specific amplification*, in express contrast to methods that use specific primers or enzymes.

G. Conclusion: The Claims Cover Only Target Capture Combined With Non-Specific Amplification

The interpretation to be given a term in a patent claim can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to include within the claim. *Wang Labs,* 197 F.3d at 1384; *Renishaw*, 158 F.3d at 1250. An inventor is entitled to claim only the invention described in the specification. Claims in a patent may not be validly construed to be broader than the supporting disclosures of the specification. *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir.1998).

The written description of the invention set forth in the patent specification is used to determine what a person skilled in the art would conclude the inventor had actually invented. *Markman,* 52 F.3d at 979. The claim construction that most naturally aligns with the patent's description of the invention will be, in the end, the correct construction. *Renishaw,* 158 F.3d at 1250.

In this case, the patent specification describes the invention of a method that combines target capture with non-specific amplification. The patent specifically teaches, as a primary benefit of the invention, that "specially tailored primers are not necessary" and that the "same standard amplification reagents can be used, regardless of the targets." Each of the examples and each of the drawings describes only amplification methods that use non-specific primers or enzymes. The inventors clearly taught that by adding specificity to a nucleic acid assay in the

target capture step, they had enabled scientists to avoid the use of specific primers and enzymes in the amplification step of the assay.

Under these circumstances, one of ordinary skill in the art as of December 1987 would have understood from the specification that the inventors' method combined target capture and non-specific amplification. This conclusion is reinforced by Dr. Lawrie's testimony that the invention was intended to provide new alternatives to sequence-specific amplification methods, such as PCR. This conclusion is made unavoidable by Dr. Richards' December 1989 description of the invention, in which he expressly contrasted the invention with other methods that use specific primers or promoters.

IV. GEN-PROBE IS ENTITLED TO SUMMARY JUDGMENT THAT ITS TMA PRODUCTS DO NOT LITERALLY INFRINGE THE CLAIMS OF THE '338 PATENT

After the claims have been construed, the next step in an infringement analysis is the comparison of the claims to the product at issue. *Carroll Touch, Inc. v. Electro Mechanical Sys., Inc.*, 15 F.3d 1573, 1576 (Fed.Cir. 1993). Here, Gen-Probe moves for summary judgment only on the issue of literal infringement. Literal infringement of a claim requires that the accused device contain each and every limitation of the claim. *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If even one claim limitation is absent from the product at issue, there can be no literal infringement as a matter of law. *See Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998).[9]

In this case, Gen-Probe's HIV-1/HCV Assay use a target-specific amplification technology called Transcription-Mediated Amplification (TMA). (Longiaru Declaration, ¶5.) TMA uses *specific* primers, *specific* promoters, and a *specific* polymerase enzyme that recognizes only those promoters. Gen-Probe's product does not use non-specific amplification. (*Id.* at ¶¶ 6-11.) Thus, the Gen-Probe product is not covered by the '338 Patent claims, which encompass only

[9] Notwithstanding the absence of literal infringement and the foregoing evidence that the inventors did not intend to claim and certainly did not invent specific amplification techniques, Vysis may yet contend that Gen-Probe's TMA products infringe the claims of the '338 patent under the doctrine of equivalents. As noted here, however, Gen-Probe has expressly limited the scope of this motion and the Court's order to the issue of literal infringement. If necessary, Gen-Probe will address the issue of the doctrine of equivalents separately.

non-specific amplification. Accordingly, as a matter of law Gen-Probe's use, manufacture and sale of this product are not within any of the claims of the '338 Patent. *See Mas-Hamilton*, 156 F.3d at 1211.

V. CONCLUSION

For the foregoing reasons, the Court should enter partial summary judgment on Counts One and Three confirming that Gen-Probe's HIV-1/HCV Assays do not literally infringe the claims of the '338 patent.

April 30, 2001

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

APPLICATION FOR EXPEDITED BRIEFING AND HEARING OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

On June 29, 2001, Vysis filed and served its Motion for Entry of Final Judgment Under Rule 54(b) ("the 54(b) Motion"). Pursuant to Local Rule 7.1(e)(1), the 54(b) Motion is set for hearing on July 30, 2001. Because of the time-sensitive nature of the relief sought in the 54(b) Motion, Vysis now seeks expedited briefing and hearing of that motion. Vysis and Gen-Probe have discussed and agreed upon a proposed briefing schedule, and Gen-Probe has indicated that it does not oppose this application for expedited briefing and hearing.

Vysis' 54(b) Motion seeks entry of final judgment as to Counts I and III of Gen-Probe's Second Amended Complaint, as well as a stay of the remaining proceedings, so Vysis may appeal the Court's grant of Gen-Probe's motion for summary judgment on noninfringement to the Court of Appeals for the Federal Circuit. Currently, the parties have numerous depositions scheduled over the next few weeks. If this Court were to grant Vysis' 54(b) Motion and stay the remaining proceedings in this case during the appeal to the Federal Circuit, those depositions could be deferred until after resolution of the appeal, or even rendered moot should the Federal Circuit affirm this Court's grant of summary judgment. Accordingly, an expedited hearing of Vysis' 54(b) Motion will allow the parties to save time and resources that might otherwise be wasted should the depositions proceed in accordance with the normal briefing and hearing schedule.

Vysis and Gen-Probe have agreed that Gen-Probe's Opposition to Vysis' 54(b) Motion would be filed by July 10, 2001, Vysis' Reply would be filed by July 13, 2001, and any hearing, if required, could be as soon after July 13, 2001 as is practicable for the Court. Further, the parties have agreed that the remaining depositions could be postponed until after Vysis' 54(b) Motion is ruled upon. The parties are aware that fact discovery is set to close on July 19, 2001, but are willing to go beyond that date until all the depositions have been completed. The parties are also willing to adjust the date on which expert reports are due to accommodate the additional time needed to complete the depositions of the fact witnesses. The parties do not seek a change of the trial date or the dates of other pretrial activities other than those relating to fact and expert discovery.

Because of the savings of time and resources that could result from an expedited hearing of Vysis' 54(b) Motion, and in light of the parties' agreement to an expedited briefing schedule, Vysis respectfully requests grant of this application. A proposed order is attached hereto.

Dated: July 2, 2001

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Gen-Probe, Incorporated v. Vysis, Inc.
United States District Court, Southern District of California, Case No. 99CV2668H (AJB)

PROOF OF SERVICE BY FAX

I, the undersigned, declare: I am over the age of 18 and not a party to the within action; I am employed in, or am a resident of, the County of San Diego, California, from which the facsimile was sent; my business address is 701 B Street, Suite 1550, San Diego, California 92101.

On July 2, 2001, at 4:04, p.m., I transmitted by facsimile the following documents:

APPLICATION FOR EXPEDITED BRIEFING AND HEARING OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

[PROPOSED ORDER GRANTING APPLICATION FOR EXPEDITED BRIEFING AND HEARING OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

Per agreement of counsel, personal service is accepted by facsimile to the party(ies) as follows:

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I further declare that the document(s) was/were transmitted by facsimile and that the transmission was reported as complete and without error. The phone number of the transmitting facsimile machine is (619) 231-6710. A copy of the transmission report which was properly issued by the transmitting facsimile machine is attached to this proof of service.

I declare under penalty of perjury that the foregoing is true and correct and that I am employed by a member of the Bar of this Court at whose direction the service was made.

Executed at San Diego, California, on July 2, 2001.

Kimberly Williams

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Gen-Probe, Incorporated v. Vysis, Inc.
United States District Court, Southern District of California, Case No. 99CV2668H (AJB)

CERTIFICATE OF SERVICE

I, the undersigned, declare: I am over the age of eighteen years and not a party to the cause; I am employed in, or am a resident of, the County of San Diego, California, and my business address is: 4665 Park Blvd., San Diego, California 92116.

On July 2, 2001, I served the following document(s):

APPLICATION FOR EXPEDITED BRIEFING AND HEARING OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

[PROPOSED ORDER GRANTING APPLICATION FOR EXPEDITED BRIEFING AND HEARING OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

by personally serving copies of said documents upon the following individuals at the following addresses or by leaving copies at the office listed below, in an envelope or package clearly labeled to identify the person being served, with a receptionist or, with a person having charge thereof:

Patrick Maloney
Stephen P. Swinton
COOLEY GODWARD, LLP
4365 Executive Drive, #1100
San Diego, CA 92121-2128

R. William Bowen, Jr.
GEN-PROBE INCORPORATED
10210 Genetic Center Drive
San Diego, CA 92121-4362

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct.

Executed on July 2, 2001 in San Diego, California.

DIVERSIFIED LEGAL SERVICES, INC.

By_____

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

[PROPOSED] ORDER GRANTING APPLICATION FOR EXPEDITED BRIEFING AND HEARING OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

Vysis' Application for Expedited Briefing and Hearing of its Motion for Entry of Final Judgment of Rule 54(b) is GRANTED. Gen-Probe's Opposition to Vysis' motion will be filed by July 10, 2001, Vysis' Reply will be filed by July 13, 2001, and the hearing on Vysis' motion will be set for oral argument on July ___, 2001.

IT IS SO ORDERED.

Date: _____

_____
JUDGE OF THE DISTRICT COURT

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.

Defendant.

Case No. 99CV 2668H(AJB)

STIPULATION RE EXPEDITED BRIEFING SCHEDULE ON VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B), [PROPOSED] ORDER THEREON

WHEREAS, on June 29, 2001, Vysis filed a Motion For Entry Of Final Judgment Under Rule 54(b) ("Vysis' Motion"); and

WHEREAS, the parties have agreed to an expedited briefing schedule on Vysis' Motion.

The parties hereby stipulate, by and through their respective counsel, that Gen-Probe's Opposition to Vysis' Motion will be filed by July 10, 2001, Vysis' Reply will be filed by July 13, 2001, and the hearing on Vysis' Motion, if required, will be as soon after July 13, 2001 as is practicable for the Court.

IT IS SO STIPULATED

Date: July 2, 2001

CHARLES E. LIPSEY (pro hac vice)
THOMAS W. BANKS (195006)
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP

By _____
Thomas W. Banks

Attorneys for Defendant
VYSIS, INC.

Date: July ___, 2001

STEPHEN P. SWINTON (106398)
J. CHRISTOPHER JACZKO (149317)
COOLEY GODWARD LLP

GEN-PROBE INCORPORATED
R. WILLIAM BOWEN, JR. (102178)

By:_____
Stephen P. Swinton

Attorneys for Plaintiff
GEN-PROBE INCORPORATED

IT IS SO ORDERED.

Vysis' Motion For Entry Of Final Judgment Under Rule 54(b) will be set for oral argument on July___, 2001.

Date: _____

_____
JUDGE OF THE DISTRICT COURT

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Attorneys for Plaintiff
Gen-Probe Incorporated

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99cv2668 H (AJB)

GEN-PROBE INCORPORATED'S OPPOSITION TO MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B)

Date: July 30, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

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Vysis seeks to suspend this case in the same manner it began – by seeking once more to have this Court stay the action for an indeterminate amount of time while it collects royalties in the interim. *See* Order Denying Motion for Stay, Ex. 1.[1] For the reasons set forth in Judge Enright's opinions in *Sure-Safe Industries, Inc. v. C&R Pier Mfg.*, 851 F.Supp. 1469 (S.D. Cal. 1993) and *Lockwood v. American Airlines, Inc.*, 1993 WL 643369 (S.D. Cal. 1993), the Court should deny Vysis' motion for entry of judgment pursuant to Federal Rule of Civil Procedure, Rule 54(b).

I. THE COURT'S ORDER GRANTING PARTIAL SUMMARY JUDGMENT DOES NOT CONSTITUTE AN COMPLETE ADJUDICATION OF ANY CLAIM IN THE ABSENCE OF A COMPLETE CONCESSION BY VYSIS ON THE DOCTRINE OF EQUIVALENTS.

The first step in consideration of a motion pursuant to Rule 54(b) is to determine whether there has been a final adjudication of any cause of action. *Curtiss-Wright Corp. v. General Elec.*, 446 U.S. 1, 7-8 (1980); *Sears, Roebuck & Co. v. Mackey*, 351 U.S. 427, 436 (1956).

In Count One of its Second Amended Complaint (Vysis' Exhibit A), Gen-Probe asserts a cause of action for declaratory judgment of non-infringement. On June 19, 2001, this Court granted partial summary judgment in this case, finding that Gen-Probe's nucleic acid test for HIV and hepatitis C virus is not covered by the literal language of the claims of the '338 patent. *See* Order Granting Motion for Partial Summary Judgment, Ex. 2. The Court's order granting partial summary judgment does not completely resolve Count One.[2] Complete determination of the issue of non-infringement requires consideration of both literal infringement *and* infringement under the doctrine of equivalents. *Roton Barrier, Inc. v. Stanley Works*, 79 F.3d 1112, 1125 (Fed. Cir. 1996). Because Gen-Probe's motion did not address the issue of infringement pursuant to the doctrine of equivalents (*See* Order Granting Partial Summary Judgment, p. 11, Ex. 2), Count One has not been completely adjudicated.

Vysis seeks to finesse this problem by stating that it "has no reasonable expectation of prevailing at trial on the issue of infringement if the Court's claim construction is sustained." *See*

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[1] All exhibits cited herein are attached to the concurrently filed Notice of Lodgment of Exhibits in Support of Gen-Probe Incorporated's Opposition to Motion for Entry of Final Judgment Under Rule 54(b).

[2] While Vysis suggests that the Court's ruling also resolves Count Three for declaratory relief, that count raises the issue of patent invalidity as well as the issue of whether the '338 patent covers Gen-Probe's products and is not resolved by the Court's order on literal infringement.

Vysis Memorandum at 2:2-4. By this statement, Vysis implicitly suggests that it is unlikely to prevail on the doctrine of equivalents. However, this oblique statement of probable outcomes is *not* sufficient to transform the Court's order into a complete adjudication of Count One. Vysis' statement does not specifically address the doctrine of equivalents, nor does it make a binding concession on that issue for purposes of Rule 54(b). Vysis' statement is therefore inadequate to fully dispose of the issue of infringement under the doctrine of equivalents. *See CAE Screenplates, Inc. v. Heinrich Fiedler GmbH & Co.*, 224 F.3d 1308, 1314-1316 (Fed. Cir. 2000).

In *CAE Screenplates*, two separate and potentially-infringing devices (the "Bar Screen" and the "Top Screen") were at issue. Defendant successfully moved for partial summary judgment of non-infringement as to the Bar Screen. 224 F.3d at 1314. In seeking entry of final judgment, plaintiff stated that the court's holding "appears to relate not only to the Bar Screen . . . but also to the Top Screen. In view of the present disposition of the case, no factual infringement issue for a jury to determine remains." *Id.* The plaintiff further stated that its submission was "not an admission that there is no infirngement, but rather a statement that it appears that if the Court interprets the claims and prosecution history as it has in its order of December 17, 1998, then the Court's decision on the Top Screen would be the same (non-infringement) as on the Bar Screen." *Id.*

The Federal Circuit concluded that CAE's concession was "non-committal" and pointed out that:

> CAE could have avoided any confusion by explicitly declaring that 'given the district court's construction of the claims, we concede non-infringement by the Top Screen plates.' Had it made this concession, no outstanding issues [concerning infringement] would remain before the district court.

224 F.3d at 1315. The court added that:

> The court is loath to sanction this type of appellate practice. The demands placed on the dockets of both this court and those of the federal district courts are severe enough without the added burden created *by uncertain concessions made by parties eager for appellate review.*

Id. (emphasis added). The Federal Circuit recognized that CAE's counsel had finally made an express, binding concession during appellate argument, which the court said would have been

"more appropriate had it been made before the district court." *Id.* at 1316.

Here, as in *CAE Screenplates*, Count One for non-infringement will not be fully resolved unless Vysis explicitly states that "Given the Court's construction of the claims of the '338 patent, Vysis concedes non-infringement under the doctrine of equivalents." An ambiguous statement that refers only to the "probability" of the ultimate outcome on the issue of infringement, and does not even reference the doctrine of equivalents, is not adequate by itself to fully resolve Count One for purposes of Rule 54(b). In the absence of a complete concession, no cause of action has been finally adjudicated and there is no partial judgment to be certified under Rule 54(b).

II. EVEN IF VYSIS CONCEDES ON THE DOCTRINE OF EQUIVALENTS, THE ADJUDICATION OF COUNT ONE SHOULD NOT BE CERTIFIED PURSUANT TO RULE 54(B).

Assuming that Vysis concedes on the doctrine of equivalents, the second question[3] raised by the present motion is whether there is "no just reason for delay" in the entry of final judgment on Count One, such that the Court should -- as a matter of discretion and sound judicial management -- grant an exception from the policy against piecemeal appeals.

The Court's order granting partial summary judgment does not determine whether the '338 patent is valid. Counts Two, Three, Four, Five and Six of Gen-Probe's Second Amended Complaint each assert that the '338 patent is invalid and Gen-Probe continues to prosecute those causes of action. (Gen-Probe is clearly entitled to show in connection with Count Four for unfair competition that Vysis threatened enforcement of a patent that not only did not cover Gen-Probe's technology, but was also invalid and/or unenforceable.) Entry of judgment on Count One under Rule 54(b), when the invalidity issues remain pending, would result in an inefficient use of judicial resources and unnecessary delay in the ultimate resolution of this case.

There is a long-standing policy in the federal courts against piecemeal disposition of litigation. *See Hohorst v. Hamburg-American Packet Co.*, 148 U.S. 262 (1893); *Woodard v. Sage Products, Inc.*, 818 F.2d 841, 845 (Fed. Cir. 1987) (en banc). Nevertheless, the drafters of the Federal Rules of Civil Procedure recognized that, in some situations, entry of partial final

[3] In *Sears*, 351 U.S. 427, the Supreme Court outlined the general framework for analysis of a motion seeking relief under Rule 54(b). First, the district court must determine whether there is a *final* judgment as to any cause of action. *Sears*, 351 U.S. at 436. Second, the district court must determine whether there is any just reason for delay in pursuing an appeal. *Id.*

judgment may be necessary "to avoid the possible injustice of a delay in judgment of a distinctly separate claim to await adjudication of the entire case." Fed.R.Civ.P. 54(b), Note of Advisory Committee on Rules, 1946 Amendment. For this reason, Rule 54(b) authorizes entry of partial final judgment in some circumstances.

However, Rule 54(b) "preserves the historic federal policy against piecemeal appeals." *Sears*, 351 U.S. at 438. The Federal Circuit has made clear that a trial court should deny a request for certification under Rule 54(b) where the moving party "has failed to disclose any 'serious, perhaps irreparable, consequence' flowing from the partial summary judgment and denial of [it's] Rule 54(b) motion." *Chaparral Communications, Inc. v. Boman Indus., Inc.*, 798 F.2d 456 (1986) *quoting Carson v. American Brands, Inc.*, 450 U.S. 79, 84 (1981); *see also Morrison-Knudsen Co. v. J.D. Archer*, 655 F.2d 962, 965 (9th Cir. 1981) ("Judgments under Rule 54(b) must be reserved for the unusual case")[4]. Therefore, piecemeal appeals remain disfavored and "it has been widely recognized that orders under [Rule] 54(b) 'should not be entered routinely or as a courtesy or accommodation to counsel.'" *Pharmacia Inc. v. Frigitonics Inc.*, 1990 U.S. Dist. Lexis 19439, at *4 (D. Mass. 1990).

Where issues of non-infringement and invalidity are presented in a patent case, the court should consider both issues and should not dispose of the case on non-infringement grounds alone. The Supreme Court has recognized the need to adjudicate both issues:

> There has been a tendency among the lower federal courts in infringement suits to dispose of them where possible on the ground of non-infringement without going into the question of validity of the patent. It has come to be recognized, however, that of the two questions, validity has the greater public importance, and the District Court in this case followed what will usually be the better practice by inquiring fully into the validity of this patent.

Sinclair & Carroll Co. v. Interchemical Co., 325 U.S. 327, 330 (1945). For this reason, the Supreme Court required the Federal Circuit to abandon its practice of vacating judgments of patent invalidity, as moot, whenever it affirmed judgments of non-infringement. *Cardinal Chemical Co. v. Morton International, Inc.*, 508 U.S. 83 (1993).

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[4] Ninth Circuit precedent controls procedural issues not related to patent law in patent cases filed in district courts within the Ninth Circuit. *CAE Screenplates Inc.*, 224 F.3d at 1314-15.

Thus, when claims of invalidity and non-infringement are presented in a case, entry of judgment on the non-infringement claim alone is generally not appropriate under Rule 54(b). *Lockwood v. American Airlines, Inc.*, 1993 WL 643369, *Sure-Safe Industries, Inc. v. C&R Pier Mfg.*, 851 F.Supp. 1469.

In both *Lockwood* and *Sure-Safe,* Judge Enright denied Rule 54(b) motions on facts and arguments nearly identical to those presented here. In *Lockwood*, the court granted summary judgment of non-infringement. Although a counterclaim for patent invalidity remained pending, plaintiff Lockwood sought to appeal immediately. Lockwood argued that the non-infringement order mooted defendants' invalidity cause of action, that the invalidity and non-infringement counts were legally and factually distinct and separable, and that it would be most efficient to allow an immediate appeal.

Judge Enright first noted that "Judgment under Rule 54(b) must be reserved for the unusual case in which the costs and risks of multiplying the number of proceedings and of overcrowding the appellate docket are outbalanced by pressing need of the litigants for an early and separate judgment." 1993 WL 643369, at *1. Citing *Cardinal Chemical Co.*, 508 U.S. 83, the court then recognized that "the Supreme Court has recently indicated its preference for that district courts rule on both the invalidity and infringement issues, even when non-infringement is found." 1993 WL 643369, at *1.

The court found that Lockwood had "presented no evidence or argument which suggests that this is an unusual case warranting relief under Rule 54(b)." The court concluded that:

> The arguments made by plaintiff are the same arguments that could be made in every patent case. In light of the direction provided by the Supreme Court in *Cardinal Chemical,* this court finds that granting plaintiff's Rule 54(b) motion would only unnecessarily delay resolution of this case.

1993 WL 643369, at *2. The Federal Circuit endorsed Judge Enright's reasoning in its opinion on related issues, noting that "our cases encourage district courts to adjudicate questions of both infringement and validity when both are raised, without reference to the order in which the are raised. The Supreme Court has expressed the same general preference." *In re Lockwood*, 50 F.3d 966, 969 n. 2 (Fed. Cir. 1995), *vacated by* 515 U.S. 1182 (1995) (citations omittted).

Similarly, in *Sure-Safe*, plaintiffs sought immediate appellate review of an order granting defendant's motion for summary judgment on plaintiff's patent infringement cause of action. Counterclaims for patent invalidity remained pending. In considering the Rule 54(b) motion, Judge Enright recognized that "[i]nterlocutory appeal should be granted only to avoid serious consequences." 851 F.Supp. at 1475. The court concluded that:

> Plaintiffs have failed to demonstrate any immediate hardship or injustice to justify a Rule 54(b) certification. Plaintiffs' request seeks to advance the convenience of the plaintiffs' and their counsel and to avoid the remote possibility of a second trial. This is not sufficient urgency to justify a Rule 54(b) certification.

Id. The court also found that an immediate interlocutory appeal would not be more efficient than first completing the entire case in the district court:

> This court disagrees that efficiencies will be gained by allowing an immediate appeal. In light of the proximity of trial, and the long delay in obtaining an appellate opinion, granting Rule 54(b) certification would not expedite the conclusion of this action. Rather, it would be more efficient to develop a full factual record and permit all the appeals to be taken at once. Finally, this court does not believe that the motion for summary judgment on infringement was incorrectly decided. Therefore, permitting a piecemeal appeal would probably be a waste of time which could be as long as two years.

Id. at 1475-76.

Vysis' reliance on *Loral Fairchild Corp. v. Victory Co.*, 931 F. Supp. 1044 (E.D.NY. 1996) is misplaced. *Loral* was a multiparty patent litigation involving "numerous" defendants and "more than 150 products and many processes." The court separated the matter into six separate trials. Following the first trial on all issues through jury verdict and post-trial motions, Judge Rader certified an immediate appeal of the judgment in that case under Rule 54(b).

Loral and this case are not comparable in any material respect. In *Loral*, *all* claims between some parties had been finally decided by trial and post-trial motions on all issues. The court decided that the result, being complete as between the parties to the first trial, should be certified prior to commencement of separate trials against other parties in the interest of judicial efficiency.

Vysis has failed to cite a single case in which a summary judgment of non-infringement has been certified under Rule 54(b) over the objection on an opposing party when invalidity issues remained pending between the parties.[5] *Lockwood* and *Sure-Safe* apply here. Issues of patent validity should be resolved prior to any appeal so that this case may be reviewed in its entirety by way of a single appeal. An immediate interlocutory appeal would only result in unnecessary delay.

III. THE EQUITIES WEIGH IN FAVOR OF RESOLVING ALL ISSUES PRIOR TO APPEAL

Consideration of whether to certify a partial judgment as final under Rule 54(b) requires the Court to consider the equities of allowing an immediate appeal. When evaluating the equities, the court may consider any factor that seems relevant to the particular case. *Angoss II Partnership v. Trifox, Inc.*, 2000 WL 288435 (N.D. Cal. May 13, 2000).

Gen-Probe is licensed under the '338 patent and has been paying royalties under a reservation of rights during the course of this litigation. *See* Declaration of R. William Bowen, and Exs. 3 and 4. Thus, as Vysis' asserts in its papers, it is in Gen-Probe's best interest to finally resolve this matter in the most expeditious manner. Gen-Probe strongly disagrees, however, that an interlocutory appeal is the quickest path to a final and complete resolution of this case.

An interlocutory appeal is likely to delay the final resolution of this matter for several years. Assuming the appellate process for such an appeal takes two years (*Sure-Safe,* 851 F.Supp at 1476), it would likely be several years more before this case is finally resolved by a trial court determination of validity issues and a subsequent appeal of those issues. Conversely, if a single appeal follows adjudication of *all* issues, this case may be finally resolved in as little as thirty months. *See e.g.* Stipulation Re Second Amended Pre-Trial Schedule; [Proposed] Order Thereon, Ex. 5 (final pretrial conference set for January 14, 2002).

While the detriment to Gen-Probe of an immediate appeal is palpable, the same is not true for Vysis. According to Vysis' moving papers, the only hardship that it will experience if it is denied the right to immediately appeal is the possibility of limited discovery and a possible re-trial

[5] There is no indication that the defendant opposed the Rule 54(b) motion referred to in *Trilogy Communications, Inc. v. Times Fiber Communications, Inc.*, 109 F.3d 739 (Fed. Cir. 1997).

if an appeal is successful. But these considerations do not justify the delay that would result from an interlocutory appeal, particularly when an appeal is unlikely to be successful. The equities clearly weigh in Gen-Probe's favor and dictate that Vysis' request for immediate entry of judgment under Rule 54(b) be denied.

IV. IN THE EVENT THE COURT CONCLUDES THAT VYSIS IS ENTITLED TO PURSUE AN IMMEDIATE APPEAL UNDER RULE 54(B), THE TRIAL ON THIS MATTER SHOULD, NEVERTHELESS, PROCEED AS PLANNED

Should the Court certify the order granting partial summary judgment as a final judgment, the Court should deny Vysis' additional request for a stay. Implicit in any order granting Vysis' motion would be a determination that there are few, if any, overlapping issues. That being so, there is no meaningful benefit in delaying the resolution of the trial of this matter.

In particular, Gen-Probe contends that the '338 patent is invalid on several grounds that are entirely independent of whether the definition of "amplification" is construed to include specific amplification. By way of example, Gen-Probe is prepared to prove through summary judgment (or trial, if necessary) that the '338 patent is invalid by reason of the inventors' failure to "enable" the practice of the claimed invention as required by 35 U.S.C. § 112. Additionally, Gen-Probe intends to prove that '338 patent is invalid because the claims are either anticipated or rendered obvious by the relevant prior art. None of these defenses depends upon the Court's determination on Gen-Probe's motion for partial summary judgment. No good reason justifies a further delay in resolving these fundamental issues.

Moreover, as discussed above, in addition to the lack of any legal or evidentiary basis to stay the trial of the remaining counts, any delay will materially prejudice Gen-Probe. Thus, if the Court is inclined to grant the Rule 54(b) certification request for any reason, it should deny Vysis' motion to stay the case. Alternatively, the Court should impose conditions that are adequate to protect Gen-Probe against the prejudice that it will suffer as a result of the delay, e.g., by conditioning its order on Vysis' agreement that payment of royalties may be made into an escrow account.

V. CONCLUSION

For the foregoing reasons, Vysis' motion should be denied.

Dated: July 10, 2001

COOLEY GODWARD LLP
STEPHEN P. SWINTON (106398)
J. CHRISTOPHER JACZKO (149317)

GEN-PROBE INCORPORATED
R. WILLIAM BOWEN, JR. (102178)

BROBECK PHLEGER & HARRISON LLP
DOUGLAS E. OLSON (38649)

By: _____
Stephen P. Swinton

Attorneys for Plaintiff
Gen-Probe Incorporated

PROOF OF SERVICE
(FRCP 5)

I am a citizen of the United States and a resident of the State of California. I am employed in (County), State of California, in the office of a member of the bar of this Court, at whose direction the service was made. I am over the age of eighteen years, and not a party to the within action. My business address is 4365 Executive Drive, Suite 1100, San Diego, California 92121-2128. On the date set forth below I served the documents described below in the manner described below:

1. **GEN-PROBE INCORPORATED'S OPPOSITION TO MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B);**
2. **DECLARATION OF J. CHRISTOPHER JACZKO IN SUPPORT OF OPPOSITION TO MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B);**
3. **DECLARATION OF R. WILLIAM BOWEN IN SUPPORT OF OPPOSITION TO MOTION FOR FINAL ENTRY OF JUDGMENT UNDER RULE 54(B); AND**
4. **NOTICE OF LODGMENT IN SUPPORT OF OPPOSITION TO MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B)**

☐ (BY U.S. MAIL) I am personally and readily familiar with the business practice of Cooley Godward LLP for collection and processing of correspondence for mailing with the United States Postal Service, and I caused such envelope(s) with postage thereon fully prepaid to be placed in the United States Postal Service at San Diego, California.

☐ (BY MESSENGER SERVICE) by consigning the document(s) to an authorized courier and/or process server for hand delivery on this date.

☐ (BY FACSIMILE) I am personally and readily familiar with the business practice of Cooley Godward LLP for collection and processing of document(s) to be transmitted by facsimile and I caused such document(s) on this date to be transmitted by facsimile to the offices of addressee(s) at the numbers listed below.

☑ (BY OVERNIGHT MAIL) I am personally and readily familiar with the business practice of Cooley Godward LLP for collection and processing of correspondence for overnight delivery, and I caused such document(s) described herein to be deposited for delivery to a facility regularly maintained by Federal Express for overnight delivery.

on the following part(ies) in this action:

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Attorneys for Vysis, Inc.

I declare that I am employed in the office of a member of the bar of this court, at whose direction this service was made.

Executed on July 10, 2001, at San Diego, California.

Marisa Salas

Marisa Salas

PROOF OF PERSONAL SERVICE

Code Civ. Proc. §§ 1011 and 1013a(1)

I hereby declare:

I am employed in the City of San Diego, County of San Diego, California; I am over the age of eighteen years and not a party to the within cause; my business address is KNOX ATTORNEY SERVICE, 2250 Fourth Avenue, San Diego, CA 92101

On July 10, 2001, I served the within document(s):

1. **GEN-PROBE INCORPORATED'S OPPOSITION TO MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B);**
2. **DECLARATION OF J. CHRISTOPHER JACZKO IN SUPPORT OF OPPOSITION TO MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B);**
3. **DECLARATION OF R. WILLIAM BOWEN IN SUPPORT OF OPPOSITION TO MOTION FOR FINAL ENTRY OF JUDGMENT UNDER RULE 54(B); AND**
4. **NOTICE OF LODGMENT IN SUPPORT OF OPPOSITION TO MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B)**

on the interested parties in this action by personally hand delivering a copy of said document(s) to the address(es) listed below:

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Fax: (619) 231-6710
Attorneys for Vysis, Inc.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct, and that this declaration was executed on July 10, 2001.

SIGNATURE: _____

PRINT NAME: _____

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Attorneys for Plaintiff
GEN-PROBE INCORPORATED

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99CV2668 H (AJB)

DECLARATION OF J. CHRISTOPHER JACZKO IN SUPPORT OF OPPOSITION TO MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B)

Date: July 30, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

I, J. CHRISTOPHER JACZKO, declare:

1. I am an attorney duly licensed to practice before this Court and am a partner with Cooley Godward LLP, attorneys of record herein for plaintiff Gen-Probe Incorporated. I am familiar with the matters set forth below based on my personal knowledge.

///

Motion for Stay and for Dismissal of Fourth Cause of Action.

3. Attached to the NOL as Exhibit 2 is a true and correct copy of the Order Granting Motion for Partial Summary Judgment of Non-Infringement of the '338 Patent; Claim Construction of the Term "Amplifying" as Found In the '338 Patent.

4. Attached to the NOL as Exhibit 5 is a true and correct copy of the Stipulation Re Second Amended Pre-Trial Schedule' [Proposed] Order Thereon

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct and that this declaration was executed by me on this 10th day of July, 2001 at San Diego, California.

J. Christopher Jaczko

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99CV2668 H (AJB)

DECLARATION OF R. WILLIAM BOWEN IN SUPPORT OF OPPOSITION TO MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B)

Date: July 30, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

I, R. William Bowen, declare as follows:

1. I am a member of the State Bar of California and admitted to practice before this Court. I am one of the counsel of record in this action for plaintiff Gen-Probe Incorporated.

2. On June 22, 1999, Gen-Probe entered into a preliminary agreement with defendant Vysis, Inc. for a royalty-bearing license of United States patent number 5,750,338 ("the '338 patent"). On August 11, 1999, Gen-Probe entered into a final agreement with defendant Vysis, Inc. for a royalty-bearing license of the '338 patent.

3. On December 21, 1999, Gen-Probe notified Vysis in writing that Gen-Probe believed the '338 patent was invalid and, further, did not cover any of Gen-Probe's products. At the same time, Gen-Probe notified Vysis in writing that it was filing this action to seek a judicial determination of the rights and obligations of the parties.

4. In February 18, 2000, Gen-Probe notified Vysis in writing that it intended to pay royalties under the license of the '338 patent pending final resolution of the causes of action asserted in this action, subject to a reservation of rights. A true and correct copy of this notice is attached as Exhibit 3 to the accompanying notice of lodgment. Gen-Probe made four quarterly royalty payments for calendar year 2000 and made the royalty payment due for the first quarter of 2001. Each of these payments was made subject to a reservation of rights. A true and correct copy of one of the letters transmitting a quarterly royalty report is attached as Exhibit 4 to the accompanying notice of lodgment.

5. The payment under the Collins patent license for the second quarter of 2001 will be due by August 30, 2001. As of the date of this declaration, Gen-Probe intends to continue making royalty payments, under a reservation of rights, pending the final resolution of all issues raised in this action.

6. On July 2, 2001, Gen-Probe inquired of Vysis's counsel whether Vysis would agree to suspend the accrual of royalty obligations, without penalty, during the pendency of any stay occasioned by its motion for 54(b) certification. Vysis's counsel stated that Vysis would not agree to the suspension of royalty payments pending interlocutory appellate review.

I hereby declare under penalty of perjury that all statements made herein of my own knowledge are true and correct.

Executed at San Diego, California on July 9, 2001.

R. William Bowen

R. William Bowen

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC., Defendant.	No. 99cv2668 H (AJB) **NOTICE OF LODGMENT IN SUPPORT OF OPPOSITION TO MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(B)** Date: July 30, 2001 Time: 10:30 a.m. Dept.: Courtroom 1

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE that Plaintiff Gen-Probe Incorporated hereby lodges the following exhibits in support of Gen-Probe Incorporated's Opposition To Motion By Defendant Vysis, Inc. For Entry Of Final Judgment Under Rule 54(b):

EXHIBIT 1: A true and correct copy of the Order Denying Motion for Stay and for Dismissal of Fourth Cause of Action;

Exhibit 2: A true and correct copy of the Order Granting Motion for Partial Summary Judgment of Non-Infringement of the '338 Patent; Claim Construction of the Term "Amplifying" as Found In the '338 Patent;

Exhibit 3: A true and correct copy of a letter dated February 18, 2000, from R. William Bowen to Norval Galloway;

Exhibit 4: A true and correct copy of a letter dated May 26, 2000, from R. William Bowen to Norval Galloway; and

Exhibit 5: A true and correct copy of the Stipulation Re Second Amended Pre-Trial Schedule; [Proposed] Order Thereon.

Dated: July 10, 2001

STEPHEN P. SWINTON
J. CHRISTOPHER JACZKO
COOLEY GODWARD LLP

DOUGLAS E. OLSON
BROBECK PHLEGER & HARRISON LLP

R. WILLIAM BOWEN, JR.
GEN-PROBE INCORPORATED

By: _____
J. Christopher Jaczko

Attorneys for Plaintiff
GEN-PROBE INCORPORATED

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

vs.

VYSIS, INC.,

Defendant.

CASE NO. 99-CV-2668 H (AJB)

Order Denying Motion for Stay and for Dismissal of Fourth Cause of Action

On January 25, 2000, the plaintiff, Gen-Probe Incorporated ("Gen-Probe") filed a first amended complaint for declaratory relief and unfair competition relating to a patent and license agreement with the defendant Vysis, Incorporated ("Vysis"). On March 9, 2000, Vysis filed a motion to stay proceedings and for dismissal of the cause of action for unfair competition. Gen-Probe filed their opposition on April 10, 2000, and Vysis filed their reply on April 17, 2000. The motion was submitted on the papers and no oral argument was held.

BACKGROUND

Gen-Probe is a biotechnology firm which develops and continues to develop diagnostic tests called genetic probes or nucleic acid tests ("NAT"). (First Am. Compl. ¶ 6-7). Gen-probe allegedly patented a certain nucleic acid technology known as "Transcription-Mediated Amplification" which enables its products to detect "extraordinarily small quantities of the nucleic acids of infectious agents." (Id. ¶ 9). In early of 1999, Vysis informed Gen-Probe that it believed that Gen-Probe's HIV and HCV blood screening products infringed claims of their United States Patent No. 5,750,338 ("'338 patent")

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(Id. ¶ 20). The '338 patent allegedly concerns probes for polynucleotide molecules such as DNA and RNA. (Id. ¶ 20).

In order to avoid any complications concerning the planned sale of its NAT test kits, Gen-Probe entered into a license agreement with Vysis concerning the '338 patent. (Id.). Under the terms of this agreement, Gen-Probe must make financial payments to Vysis for royalties of the sale of any products covered by the '338 patent. (Id. ¶ 21).

Gen-Probe now alleges that the '338 claims are invalid and that their NAT tests would not infringe on the '338 patent if the claims were valid. In its complaint, Gen-Probe asserts the following causes of action: (1) non-infringement of the '338 patent; (2) invalidity of the '338 patent; (3) declaratory relief concerning the licensing agreement between the parties; and (4) a state court unfair competition claim under California Business and Professions Code section 17200, *et seq.*

DISCUSSION

I. Request for Stay

Vysis argues that the matter should be stayed pending a reissue application of the '338 patent with the United States Patent and Trademark Office ("PTO"). In considering a motion for stay, a Court must weigh the benefits resulting from the reissue process against the hardships and prejudice that a stay will cause on the parties. See Xerox v. 3Com Corp., 69 F. Supp. 2d 404, 406-07 (W.D.N.Y. 1999).

In this matter, Gen-Probe contends that the '338 patent is invalid. Vysis asserts that because the PTO will consider the reissue application in light of Gen-Probe's assertions that the patent is invalid, a stay would further "interests of judicial economy" and the Court would benefit from the PTO's expertise and conclusions concerning the reissue application. However, the validity of a patent cannot be based solely on the decisions of the PTO and the Court must still rule on the validity of the patent. See Quad Environmental Tech v. Union Sanitary Dist., 946 F.2d 870, 875 (Fed. Cir. 1991) (holding that courts are the final arbiters of patent validity and must decide without deference to the rulings of the patent examiner).

Furthermore, there is no way to determine the length of time required for the PTO to examine the reissue patent application. The parties disagree on whether the expedited status of reissue

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applications would guarantee its resolution within a year and the PTO's procedures concerning the examination of the application are beyond the Court's control.

Consequently, the Court DENIES the request for a stay at this time.

II. **Motion to Dismiss the Cause of Action for Unfair Competition**

Pursuant to Federal Rule of Civil Procedure 12(b)(6), Vysis also moves to dismiss the fourth cause of action for unfair competition under California Business and Professions Code section 17200, *et seq.* To prevail on this claim, Vysis must show that "the plaintiff can prove no set of facts in support of [its] claim that would entitle [it] to relief." See Schneider v. California Department of Corrections, 151 F.3d 1194, 1996 (9th Cir. 1998). Furthermore, the Court must accept the facts that Gen-Probe asserts in its complaint as true. See Cooper v. Pickett, 137 F.3d 616, 623 (9th Cir. 1997). Section 17200 proscribes unlawful, unfair or fraudulent business practices or conduct. See Cel-Tech Communications, Inc. v. Los Angeles Cellular Telephone Co., 20 Cal.4th 163, 180 (1999).

Gen-Probe alleges that Vysis "knows or should know the underlying facts establishing the validity of the . . . '338 patent." (First Am. Compl. ¶ 35). Gen-Probe also alleges that Vysis continues to attempt to enforce this patent despite its knowledge that the patent is invalid. (Id.). The Court finds that these allegations sufficiently allege a cause of action under Federal Rule of Civil Procedure 12(b)(6). Consequently, the motion to dismiss is DENIED.

CONCLUSION

The Court DENIES the motion for a stay. The Court also DENIES the motion to dismiss the fourth cause of action.

IT IS SO ORDERED.

DATED: 4/28/00

MARILYN L. HUFF, CHIEF JUDGE
UNITED STATES DISTRICT COURT

EXHIBIT 1

Copies to:

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EXHIBIT 1

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Clerk

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, vs. VYSIS, INC., Defendant.	CASE NO. 99-CV- 2668 H (AJB) **Order Granting Motion for Partial Summary Judgment of Non-Infringement of the '338 Patent; Claim Construction of the term "Amplifying" as found in the '338 Patent**

On March 13, 2001, plaintiff Gen-Probe, Incorporated filed a Second Amended Complaint for declaratory relief and unfair competition related to a patent and license agreement with the defendant Vysis, Incorporated. This case is styled as a declaratory judgment action brought by Gen-Probe. Thus, Vysis, the owner of U.S. Patent No. 5,750,338 ("the '338 patent"), is the defendant. Gen-Probe asks the Court to declare the '338 patent invalid and further declare that Gen-Probe's current and anticipated activities do not infringe any valid claims of the '338 patent. In its Second Amended Complaint, Gen-Probe asserts the following causes of action: (1) non-infringement of the '338 patent; (2) invalidity of the '338 patent; (3) declaratory relief; (4) unfair competition; (5) unenforceability of the '338 patent.

On April 30, 2001, Gen-Probe filed a motion for partial summary judgment under Counts One and Three of its Second Amended Complaint arguing that its nucleic acid test for human immunodeficiency virus ("HIV") and hepatitis C virus ("HCV") does not literally infringe the claims

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of the '338 patent held by Vysis. Specifically, Gen-Probe argues that the '338 patent describes and encompasses only methods of non-specific amplification and that its products do not incorporate non-specific amplification.

On May 25, 2001, Vysis filed its Opposition. On June 1, 2001, Gen-Probe filed its Reply. The Court held a hearing on the motion and claim construction for the term "amplifying," as found in Claims of the '338 Patent, on June 7, 2001. R. William Bowen and Stephen Swinton appeared on behalf of Gen-Probe and Charles Lipsey, John L'Estrange appeared on behalf of Vysis. Thomas Banks and Scott Orwell appeared telephonically on behalf of Vysis.

I. Scientific Background

The '338 patent relates generally to methods for use in nucleic acid diagnostics, including the use of nucleic acid "probes" to detect infectious organisms. The '338 patent describes methods by which nucleic acids may be "captured" onto solid supports and "amplified," so that small quantities of nucleic acids may be then detected by the probes.

"Target capture" techniques are used in nucleic acid methods to isolate a particular nucleic acid of interest prior to detection or other steps. In target capture methods, the target nucleic acid is bound to a solid support, such as a filter, particle, or bead, which allows the target to be removed from the sample in which it was originally contained.

In order to achieve a detectable level of target organisms in a sample, it is sometimes necessary to increase the target organism's nucleic acid through processes known as "nucleic acid amplification" by using enzymes and primers. "Polymerase" enzymes are used to copy a DNA or RNA strand and make its compliment. Primers are short pieces of DNA that are used in amplification methods to cause an enzyme, such as DNA polymerase, to start its copying at a certain point along a nucleic acid sequence. Like probes in the detection step, primers work by binding to a complementary nucleotide sequence in the target nucleic acid. Primers can either be specific or non-specific. Specific primers are designed to bind only to a pre-selected nucleic acid sequence. Non-specific or "random" primers can be used with DNA polymerase to copy random portions of the nucleic acid sequence of the target organism.

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II. The '338 Patent

The '338 patent contains six independent claims (claims 1, 7, 19, 27, 28, and 34). Each of these claims is generally directed to a method of, or kit for, capturing the target (i.e. binding a support to the target polynucleotide and substantially separating the support and bound target from the sample) and "amplifying" a target polynucleotide. Each independent claim contains the term "amplifying." For example, claim 1 provides:

> A method for amplifying a target polynucleotide contained in a sample comprising the steps of: (a) contracting the sample with a first support which binds to the target polynucleotide; (b) substantially separating the support and bound target polynucleotide from the sample; (c) amplifying the target polynucleotide.

The '338 patent specification sets forth seven examples of the methods taught by the inventors. The first three examples refer only to methods of target capture alone. Examples four through seven refer to combining target capture and methods of amplification.

III. Standard of Review

A. Motion for Summary Judgment

A motion for summary judgment shall be granted where "there is no genuine issue as to any material fact and . . . the moving party is entitled to judgment as a matter of law." Fed.R.Civ.P. 56(c); See also British Airways Bd. v. Boeing Co., 585 F.2d 946, 951 (9th Cir. 1978), cert. den., 440 U.S. 981 (1979). Determination of infringement is a two-step procedure. First, the claims are construed by the Court as a matter of law. Second, the properly construed claims are applied to the accused device, a question of fact. See Wang Laboratories, Inc. v. America Online, Inc., 197 F.3d 1377, 1380 (Fed. Cir. 1999); EMI Group North America, Inc. v. Intel Corp., 157 F.3d 887, 891 (Fed Cir 1998).

B. Claim Construction

Claim construction is an issue of law to be decided by the Court. Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996). "[T]he focus in construing disputed terms in claim language is not the subjective intent of the parties to the patent contract when they used a particular term. Rather the focus is on the objective test of what one of ordinary skill in the art at the time of the invention would have understood the term to mean." Id. at 985-86.

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When construing the terms of a patent, the Court must first turn to "intrinsic evidence." Intrinsic evidence includes the claim itself, the specification, and the prosecution history of the patent. Vitronics Corp. v. Conceptronic, Inc., 90 F. 3d 1576, 1582 (Fed. Cir. 1996). Established rules of claim interpretation require that the Court first consider the words of the claims themselves, "both asserted and unasserted, to define the scope of the patented invention." Id. at 1582. The words are generally given their customary and ordinary meaning. Id.; Hoechst Celanese Corp. v. BP Chemicals, Ltd., 78 F.3d 1575, 1578 (Fed. Cir. 1996) (stating that in defining technical terms, the Court should interpret it "as having the meaning it would be given by persons experienced in the field of the invention"). However, the Court must follow the definition of terms intended by the patentee if his or her special definition is clearly delineated in the specification or file history. Vitronics Corp., 90 F.3d at 1583; Hoechst Celanese Corp., 78 F.3d at 1578.

The Court also considers the specification to determine whether the inventor has employed any terms or words in a manner that is inconsistent with their plain and ordinary meaning. Vitronics, 90 F.3d at 1582. "Claims must be read in view of the specification, of which they are a part." Markman, 52 F.3d at 979. "One purpose for examining the specification is to determine if the patentee has limited the scope of the claims." Watts v. XL Sys., Inc., 232 F.3d 877, 882 (Fed. Cir. 2000).

The Court also may review the prosecution history of the patent, if admitted into evidence. Vitronics, 90 F.3d at 1582. This history is "the complete record of all the proceedings before the Patent and Trademark Office, including any express representations made by the applicant regarding the scope of the claims." Id. It also includes prior art which is cited in the file history. Id. at 1583.

The Court may resort to extrinsic evidence only if the intrinsic evidence is considered and there still remains some ambiguity as to the scope or meaning of the claim. Id. at 1583. "[I]deally there should be no 'ambiguity' in claim language to one of ordinary skill in the art that would require resort to evidence outside the specification and prosecution history." Markman, 52 F.3d at 986. Extrinsic evidence can include any evidence outside the patent and prosecution history such as prior art documents, dictionaries, technical treatises, articles, expert testimony, and inventor testimony. Vitronics, 90 F.3d at 1584. However, "extrinsic evidence in general, and expert testimony in

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particular, may be used only to help the court come to the proper understanding of the claims; it may not be used to vary or contradict the claim language." Id.

IV. Analysis

Gen-Probe argues that it is entitled to summary judgment of non-infringement because its product (the HIV/HCV Assay) uses only specific amplification. Gen-Probe asserts that the term "amplifying" as used in the '338 patent would be understood by one of ordinary skill in the art at the time of the invention to encompass only non-specific amplification. Vysis agrees that Gen-Probe's product uses specific amplification. However, Vysis contends that the '338 patent is not limited to non-specific amplification.

A. Claim Construction

In construing the term "amplifying" of the '338 patent, the Court must first turn to "intrinsic evidence." Intrinsic evidence includes the claim itself, the specification, and the prosecution history of the patent. The claim language in this case does not help determine the construction of the term "amplifying." The term "amplifying" is found in each of the principle claims without any modification.

1. Specification

Gen-Probe argues that the specification of the '338 patent supports a construction of "amplifying" to only include non-specific amplification. The Court agrees. Immediately before the Examples that teach amplification in the '338 patent, the inventors set forth their teachings with respect to amplification methods.

> The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by **non-specific replication** using standard enzymes...In addition, where amplification is employed following purification of the target nucleic acids as described above, the amplified nucleic acids can be detected according to other, conventional methods not employing the [techniques] described above. Amplification of the target nucleic acid sequences, because it follows purification of the target sequences can employ **non-specific enzymes or primers** (i.e. enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence). Although any background, non-target nucleic acids are replicated along with target, this is not a problem because most of the background nucleic acids have been removed in the course of the capture process. Thus **no specially tailored primers are needed** for each test, and the same standard amplification reagents can be used regardless of the targets.

'338 patent, col. 30, lines 14-40 (emphasis added).

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The introduction to the amplification techniques only addresses the possibility of using non-specific amplification methods. Vysis argues that the language permissive such that while "non-specific" methods "can be" used, they need not be. Vysis concedes that it did not invent specific or non-specific amplification. Rather, Vysis argues that its contribution to the science was the idea of target capture plus amplification. Vysis states that the patent focuses on the combination of the two, not describing amplification methods. Without target capture prior to amplification, non-specific amplification would not be a viable technique for detecting target nucleic acids in a sample. Vysis argues that the specification tells those of ordinary skill in the art that, while the use of target capture made it possible to use non-specific amplification in assays for detecting nucleic acids, the invention was more generally directed to the use of target capture prior to either specific or non-specific amplification. However, if the inventors wanted to teach that either method could be used they could have included at least one sentence or reference to specific amplification. They did not.

Vysis contends that a parenthetical sentence in Example 5 of the Specification does explicitly set forth the idea of specific amplification. The Specification of the '338 patent includes four Examples which teach the amplification techniques disclosed in the patent. Vysis agrees that Examples 4, 6 and 7 only teach non-specific amplification.[1] The parties dispute the proper interpretation of the description set forth in Example 5 of the Specification. Example 5 provides:

> In this example, both non-specific replication of target DNA and transcription of that DNA are used to amplify capture DNA. Referring to FIG. 5, ...Because the primers are random, some will, simple as a matter of statistics, bind to and cause replication of sample sequences, no matter what those sequences are. (Alternatively, the double stranded DNA can be formed by synthesis starting from capture probe a.)

'339 patent, col. 31, lines 24-26, 44-48.

Vysis contends that the parenthetical disclosure indicates that the capture probe is used as a specific primer to the target DNA and thus discloses "specific amplification." However, the explicit language of Example 5 (i.e. "non-specific replication" and "random" primers) refers only to non-specific amplification. In addition, Example 5 incorporates Figure 5, of the drawings in the patent.

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[1] For example, Example 4 describes a method of non-specific amplification using polymerases that lack transcriptional specificity ('338 Patent, col. 30, lines 59-68) and Example 6 describes amplification using random hexamer primers to "bring about non-specific double-stranded DNA synthesis." ('338 patent, col. 31, lines 57-64).

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In discussing Figure 5, the inventors state, "In Step 3 of FIGS. 4, 5 and 6, the isolated target is non-specifically amplified to form a multitude of amplification products."

The words "specific amplification" or "PCR" do not appear in the Specification of the '338 patent. Vysis contends this is because the term "amplifying" was always used and meant to be used in its broadest sense, which includes both specific and non-specific amplification. However, the Federal Circuit has made clear that although the specification of a patent need not present every embodiment of the invention and the claims are not limited to the preferred embodiment of the invention, the claims can not enlarge what is patented beyond what the inventor has described as the invention. See Wang Laboratories, Inc. v. America Online, Inc., 197 F.3d 1377, 1383 (Fed. Cir. 1999); SciMed Systems, Inc. v. Advanced Cardiovascular Systems, Inc., 242 F.3d 1337, 1341 (Fed. Cir. 2001).

In Wang Labs, the Federal Circuit determined that although the term "frame" had meaning in general usage that encompassed both bit-mapped and character-based protocols, the specification only described and taught character-based display frames. Thus, the Court limited the claims to the only teaching set forth in the embodiment. In reaching its conclusion, the Court held that claims should not be interpreted to have a meaning or scope that would lead to their invalidity. Wang Labs, 197 F.3d at 1382-83. The Court held that the requirements of 35 U.S.C. § 112 (written description and enablement) could not be met with respect to protocols other than character-based frames. Id.

In this case, a motion for invalidity pursuant to 35 U.S.C. § 112 is not before the Court. However, the specification of the '338 patent does not describe specific amplification methods and does not teach any benefits from the combination of target capture and specific amplification. In fact, the specification teaches that you do not need to do specific amplification. The specification refers to specially tailored primers only to state that they are not necessary when an initial target capture step is used. In addition, Example 5 teaches non-specific replication of target DNA using random primers and non-specific transcription. The parenthetical reference to an "alternative" method, does not teach that such a method constitutes specific amplification or that the capture probe functions as a specific primer. The plain reading of Example 5 and Figure 5 is that they teach non-specific amplification. The Court will try to construe claims, when feasible, to sustain their validity. The Court finds it

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difficult to construe "amplifying" to include specific amplification based on the disclosures in the specification that would satisfy the written description requirement of 35 U.S.C. § 112.

Recently the Federal Circuit in SciMed Systems stated, "[w]here the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question." SciMed, 242 F.3d at 1341. The Court concludes that the specification supports Gen-Probe's contention that the term "amplifying" as used in the '338 patent only encompasses non-specific amplification.

2. Prosecution History

Vysis contends that the prosecution history makes clear that both the patent owner and the PTO considered the claimed invention to include PCR, a type of specific amplification. The original claims of the '338 patent were rejected by the PTO, citing the PCR patents. Vysis argues that this must mean that the PTO understood the '338 patent to include specific amplification techniques. Vysis also points to a response by the patent owner to the PTO, indicating that "[t]argets can be amplified by a number of ways including PCR." Banks Decl., Ex. E, p. 18. Finally, in the Examiner's Statement of Reasons for Allowance the Patent Examiner states, "[t]he claims are drawn to methods of PCR amplification wherein the target is first separated from the sample by using a support that binds to the target polynucleotide and then amplified." Banks Decl., Ex. F, p. 2.

Vysis argues that the Patent Examiner's understanding of the meaning of patent claims developed during prosecution is relevant to construing the proper scope and meaning of those terms. See Markman, 52 F.3d. At 983.

Gen-Probe asserts that the rejection by the PTO of the patent application based on the Mullis (PCR) patent does not support the claim that the patent covered PCR amplification methods. Vysis acknowledged in oral argument that did not have a license to the Mullis patents or PCR method. Gen-Probe argues that the patent application was rejected as obvious in light of the PCR patents because specific capture methods plus non-specific amplification were an attempt to achieve the same results as PCR. Gen-Probe also contends that statements made by the patent owner to the Patent Examiner in 1995, eight years after the application was first filed, were made too late to determine how a person

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skilled in the art would have understood the invention as of the date of filing.

The focus of claim construction is how a person skilled in the art would have understood the claimed invention in the patent at the time of filing. Markman, 52 F.3d at 985-986. The prosecution history indicates that the patent application was rejected at least three times by the PTO for being obvious in light of a combination of target capture and amplification patents, including the Mullis (PCR) patents. However, despite the fact that the patent owner was clearly aware PCR, it failed to explicitly include specific amplification methods in the teachings of the patent. The prosecution history does not help explain this omission.

The Court concludes that the references to the Mullis patents and PCR in the prosecution history do not help clarify the proper construction of the term "amplifying" as used in the '338 patent. At most, the prosecution history indicates that the idea of amplification by first using specific target capture techniques is close enough to the goals of PCR to be "obvious" to the PTO in light of the Mullis patents.[2]

3. Extrinsic Evidence

Gen-Probe argues that the inventor's own testimony about the scope and intent of the patent confirms that "amplifying" includes only non-specific amplification. The Court only uses extrinsic evidence to help it come to the proper understanding of the claim terms. The Court will not use extrinsic evidence to vary or contradict claim terms. See Vitronics, 90 F.3d at 1584.

Gen-Probe has submitted testimonial and documentary evidence from the inventors of the '338 patent. Gen-Probe highlights the testimony of inventor Jon Lawrie. Lawrie stated that the '338 patent, "was directed to methods separate from PCR." Lawrie Depo. at 178:19-180:11. Similarly, inventor Walter King testified that specific amplification was not discussed at the meeting of the inventors in 1986 because the objective was to find an alternative to PCR. King Depo. at 184-186. King stated, "I think that at the highest level we were looking for amplification methods that did not involve PCR amplification." King Depo. at 45:10-15. King also testified that he did not understand the inventors

[2] In addition, an early drawing by inventor Jon Lawrie indicates that he was concerned that the use of "specific capture and non-specific amplification" was "too close" to the PCR method invented by Mullis and others at Cetus Corp (Exh. 12).

EXHIBIT 2

to be claiming as their invention a combination of target capture and specific amplification. King Depo. at 136:14-21.

Gen-Probe also points to a letter written by Dr. James Richards, Director of Business Development and Licensing for Gene-Trak Systems, to one of Gene-Trak's partners stating:

> Cetus, Sibia/Salk, Biotechnica, etc. all claim specific primers for amplification whereas the present invention claims uses of the opposite, namely non-specific primer or promoters...Following extensive washing, captured target polynucleotides could be released and the non-specific amplification process could take place.

Jaczko Decl., Ex. 1, pg. 2.

Vysis argues that the testimony former employees of Vysis' predecessor company Gene-Trak Systems should be given no weight because there can be "significant difference between what an inventor thinks his patented invention is and what the ultimate scope of the claims is after allowance by the PTO." Markman, 52 F.3d at 985. However, Vysis' argument is more appropriately raised when inventor try to expand the scope of the patent claims by testifying about their subjective intent, over the description set forth in the specification. In this case, the specification supports a construction of the term "amplifying" to include only non-specific amplification and the inventors' testimony supports this construction.

While the Court does not use extrinsic evidence to construe claim terms, the evidence offered by Gen-Probe helps explain the context of the '338 patent. In particular, the inventor's testimony and the Richards' letter explain why there is no explicit reference in the specification to amplification using PCR. The extrinsic evidence in this case supports the conclusion that one of ordinary skill in the art at the time of the invention would have understood the term "amplifying" to mean non-specific amplification.

Based on the explicit language of the specification, the repeated reference to non-specific amplification methods, and the absence of any reference to specific amplification or PCR, the Court construes the term "amplifying" as found in the claims of the '338 patent to encompass only non-specific amplification. The Court finds that one of ordinary skill in the art as of December 1987 would have understood from the specification that the inventors' method combined target capture and non-specific amplification. This conclusion is reinforced by the inventors' testimony and the Richards' letter.

EXHIBIT 2

B. Infringement

After construing the term "amplifying" the Court can turn to question of literal infringement. Literal infringement requires that the accused device contain each limitation of the claim. Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1247 (Fed. Cir. 2000). In this case, Gen-Probe's Assay uses a target-specific amplification technology. Vysis admits that Gen-Probe's product uses specific amplification. There is no issue of material fact which would prevent the Court from ruling on infringement in a motion for summary judgment. Since the Court has construed the term "amplifying" to encompass only non-specific amplification, the Court concludes that Gen-Probe does not literally infringe the claims of the '338 patent.

V. Conclusion

For the reasons set forth above, the Court GRANTS Gen-Probe's Motion for Partial Summary Judgement of non-infringement of the claims of the '338 patent.

IT IS SO ORDERED.

DATED: 6/19/01

MARILYN L. HUFF, Chief Judge
UNITED STATES DISTRICT COURT

Copies to:

Stephen Swinton
Cooley Godward LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121

Charles Lipsey
Finnegan, Henderson, Farabow, Garrett & Dunner
1300 I Street, N.W., Suite 700
Washington, D.C. 20005

EXHIBIT 2

EXHIBIT 3

GEN-PROBE

February 18, 2000

R. William Bowen, Jr.
Vice President & General Counsel
(858) 410-8918
(858) 410-8637 (facsimile)
E-mail: billb@gen-probe.com

By Facsimile

Norval B. Galloway, Esq.
Patent Counsel
VYSIS, INC.
3100 Woodcreek Drive
Downers Grove, Illinois 60515

Dear Norval:

This letter responds to your letter of February 11, 2000.

First, I have received the draft licenses and forwarded them to Chiron and Bayer for review. I hope to be able to provide collective comments in the near future. I apologize for the delay in forwarding the licenses to Chiron and Bayer, but I was unaware that Pete had received the drafts from you when they were first sent. I did not see them until you resent them. We consider the licenses to be in effect as of December 21, 1999 (subject to the logistical step of completing the documentation) and will proceed accordingly.

Second, as to license royalties, I can report as follows. Gen-Probe is not now selling any product arguably covered by the original license to Gen-Probe. We anticipate commencing U.S. clinical trials of our Combo 2 product for the detection of *Neisseria gonorrheae* and *Chlamydia trachomatis* before the end of March. We anticipate that the product will be launched commercially by the end of the year. This product uses a form of target capture and a form of target amplification. Without waiving the claims asserted in our complaint for declaratory relief as to validity and non-infringement, and specifically reserving our rights in connection with those claims, it is our current intention to treat the Combo 2 product -- upon its commercial introduction -- as subject to the Collins License pending the resolution of the lawsuit.

Gen-Probe understands that Chiron is now selling the HIV/HCV blood screening assay in France following regulatory approval. An approved product is not being sold anywhere else in the world at this time. The HIV/HCV blood screening assay uses a form of target capture and a form of target amplification. Without waiving the claims asserted in our complaint for declaratory relief as to validity and non-infringement, and specifically reserving our rights in connection with those claims, it is our current intention to treat commercial sales of the HIV/HCV blood screening assay as subject to the Collins License pending the resolution of the

EXHIBIT 3

lawsuit. The first royalty report will be due as of March 1 and we we expect to submit a timely report. Any royalty report and/or royalty payment which includes sales of any product in foreign countries prior to approval of that product for sale in the United States will specifically reserve our rights pursuant to 35 U.S.C. § 271(e) and will not waive those rights.

Bayer handles the distribution of the clinical diagnostic products. Bayer is not now selling any product arguably covered by the license. We anticipate that U.S. clinical trials for an HCV product will be commenced before the end of the year and it also possible that ASR products may be sold this year. The HCV assay will use a form of target capture and a form of target amplification. Without waiving the claims asserted in our complaint for declaratory relief as to validity and non-infringement, and specifically reserving our rights in connection with those claims, it is our current intention to treat the HCV diagnostic product -- upon its commercial introduction -- as subject to the Collins License pending the resolution of the lawsuit.

Third, because we intend to treat the above-referenced products as covered by the license, pending the determination of our complaint for declaratory relief, it is my understanding that all such products sold commercially will be marked in accordance with Gen-Probe's standard marking practices with respect to its own patents. At present, based on the advice of counsel, Gen-Probe does not mark its patent numbers on products sold in any countries other than the United States, Canada, and Australia. Without waiving the claims asserted in our complaint for declaratory relief as to validity and non-infringement, and specifically reserving our rights in connection with those claims, we intend to include the Collins U.S. patent numbers on products sold commercially in the United States pending the resolution of the lawsuit.

Fourth, and finally, my letter to you requesting notice of any post-patent applications to the PTO was in fact misdated and should have been dated February 10 rather than December 21. As you requested, I am enclosing a corrected copy of the letter for your records.

I will forward comments on the licenses as soon as I have collected them. Thank you for considering these matters. Please call me if you would like to discuss any of them.

Sincerely,

R. William Bowen, Jr.
Vice President and General Counsel

EXHIBIT 39

GEN-PROBE

May 26, 2000

R. William Bowen, Jr.
Vice President & General Counsel
(858) 410-8918
(858) 410-8637 (facsimile)
E-mail: billb@gen-probe.com

By Facsimile and FedEx

Norval B. Galloway, Esq.
Patent Counsel
VYSIS, INC.
3100 Woodcreek Drive
Downers Grove, Illinois 60515

Dear Norval:

This letter is the royalty report pursuant to the Collins licenses for the first quarter of 2000 and includes a revised report for 1999.

I have previously informed you that, without waiving the claims asserted in our complaint for declaratory relief as to validity and non-infringement, and specifically reserving our rights in connection with those claims, it is our current intention to treat commercial sales of the HIV/HCV blood screening assay as subject to the Chiron/Gen-Probe license pending the resolution of the lawsuit. Subject to the same conditions, it is our current intention to treat commercial sales of the qualitative HBV and HCV diagnostic assay as subject to the licenses pending the resolution of the lawsuit.

The information required by the license is set forth in the enclosed summary. Payment of the royalties due for the first quarter of 2000 and for the revised report for 1999 is enclosed.

For your information, the HIV/HCV blood screening assay has received regulatory approval in the following countries: France (Sept. 21, 1999); Spain (Feb. 2, 2000); and Australia (March 31, 2000).

As set forth in a separate, accompanying letter, Gen-Probe and Chiron reserve all rights with respect to sales in or to France prior to regulatory approval.

Please call me if you would like to discuss this matter.

Sincerely,

R. William Bowen, Jr.

EXHIBIT 4

ORIGINAL

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.

Defendant.

Case No. 99CV 2668H(AJB)

STIPULATION RE SECOND AMENDED PRE-TRIAL SCHEDULE; [PROPOSED] ORDER THEREON

WHEREAS, on March 12, 2001, the Court issued an Order Re Amended Pre-Trial Schedule setting the remaining pre-trial schedule:

WHEREAS, counsel for Vysis, Thomas Banks, informed counsel for Gen-Probe that Mr. Banks presently has a lower back disc injury that may require surgery, and his physician has advised him not to travel;

WHEREAS, Vysis wishes to take eleven additional depositions of Gen-Probe employees and Gen-Probe wishes to take four additional depositions of Vysis and third party employees before the close of discovery presently set for June 19, 2001;

WHEREAS, Vysis will have to bring into the case another lawyer from Finnegan, Henderson to replace Mr. Banks; and

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EXHIBIT 5

WHEREAS, counsel for the parties have met and conferred and Gen-Probe has no objections to a one month extension of time to the present amended pre-trial schedule.

The parties hereby stipulate, by and through their respective counsel, to a one month extension in accordance with the following second amended pre-trial schedule:

1. The deadline for each party to comply with the opening disclosure report provisions in Rule 26(a)(2)(A) and (B) of the Federal Rules of Civil Procedure shall be extended from June 22, 2001 to July 23, 2001. The deadline for any opposing reports to be exchanged shall be extended from July 18, 2001 to August 20, 2001.

2. The deadline for any party to supplement its disclosure regarding contradictory or rebuttal evidence under Rule 26(a)(2)(c) shall be extended from July 30, 2001 to August 30, 2001.

3. The parties are aware that the failure to comply with this section or any other discovery order of the court may result in the sanctions provided for in Fed.R.Civ.P. 37 including a prohibition on the introduction of experts or other designated matters in evidence.

4. The deadline for all fact discovery to be completed shall be extended from June 19, 2001 to July 19, 2001. The deadline for all expert discovery to be completed shall be extended from August 15, 2001 to September 17, 2001. The parties are aware that the term "completed" means that all discovery under Rules 30-36 of the Federal Rules of Civil Procedure, and discovery subpoenas under Rule 45, must be initiated a sufficient period of time in advance of the cut-off date, *so that it may be completed* by the cut-off date, taking into account that times for service, notice and response as set forth in Federal Rules of Civil Procedure. The parties also understand that the court requires that *all discovery conferences must be calendared within 30 days of the dispute arising*.

5. The deadline for hearing all other pretrial motions shall be extended from October 9, 2001 to November 9, 2001.

6. The deadline for counsel for file their Memoranda of Contentions of Fact and Law and take any other action required by Local Rule 16.1(f)(3) shall be extended from November 13, 2001 to December 13, 2001.

EXHIBIT 5

7. The deadline for counsel to comply with the Pre-trial disclosure requirements of Federal Rule of Civil Procedure 26(a)(3) shall be extended from November 12, 2001 to December 12, 2001.

8. The deadline for counsel to meet and take the action required by Local Rule 16.1(f)(5) shall be extended from November 26. 2001 to December 26. 2001.

9. The deadline for filing objections to Pre-trial disclosures shall be extended from December 3, 2001 to January 3, 2002.

10. The deadline for preparation, service and lodging of the Proposed Final Pretrial Conference Order required by Local Rule 16.1(f)(7) shall be extended from December 3, 2001 to January 7, 2002.

11. The Final Pretrial Conference set on the calendar of Judge Huff on December 10, 2001 at 10:30 a.m. shall be vacated and reset for January 14, 2002 at 10:30 a.m.

12. A post-trial settlement conference before a magistrate judge may be held within 30 days of verdict in the case.

13. The dates and times set forth herein will not be modified except for good cause shown.

14. Dates and times for hearings on motions should be approved by the Court's clerk before notice of hearing is served.

15. Briefs or memoranda in support of or in opposition to any pending motion shall not exceed twenty-five (25) pages in length without leave of a district court judge. No reply memorandum shall exceed ten (10) pages without leave of a district court judge. Briefs and memoranda exceeding ten (1) pages in length shall have a table of contents and a table of authorities cited.

EXHIBIT 5

IT IS SO STIPULATED

Date: May 30 2001

CHARLES E. LIPSEY (pro hac vice)
THOMAS W. BANKS (195006)
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP

By _____
Thomas W. Banks

Attorneys for Defendant
VYSIS, INC.

Date: May 30, 2001

STEPHEN P. SWINTON (106398)
J. CHRISTOPHER JACZKO (149317)
COOLEY GODWARD LLP

GEN-PROBE INCORPORATED
R. WILLIAM BOWEN, JR. (102178)

By: _____
J. Christopher Jaczko

Attorneys for Plaintiff
GEN-PROBE INCORPORATED

[PROPOSED] ORDER

IT IS SO ORDERED.

Date: 6/4/01

_____
ANTHONY J. BATTAGLIA
United States Magistrate Judge

EXHIBIT 5

PROOF OF SERVICE
(FRCP 5)

I am a citizen of the United States and a resident of the State of California. I am employed in San Diego, State of California, in the office of a member of the bar of this Court, at whose direction the service was made. I am over the age of eighteen years, and not a party to the within action. My business address is 4365 Executive Drive, Suite 1100, San Diego, California 92121-2128. On the date set forth below I served the documents described below in the manner described below:

1. STIPULATION RE SECOND AMENDED PRE-TRIAL SCHEDULE; [PROPOSED] ORDER THEREON

☐ (BY U.S. MAIL) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of correspondence for mailing with the United States Postal Service, and I caused such envelope(s) with postage thereon fully prepaid to be placed in the United States Postal Service at Palo Alto, California.

☐ (BY MESSENGER SERVICE) by consigning the document(s) to an authorized courier and/or process server for hand delivery on this date. See attached Proof of Personal Service.

☐ (BY FACSIMILE) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of document(s) to be transmitted by facsimile and I caused such document(s) on this date to be transmitted by facsimile to the offices of addressee(s) at the numbers listed below.

☑ (BY OVERNIGHT MAIL) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of correspondence for overnight delivery, and I caused such document(s) described herein to be deposited for delivery to a facility regularly maintained by Federal Express for overnight delivery.

on the following part(ies) in this action:

EXHIBIT 5

4106 2118 3292

Thomas W. Banks Esq.
Finnegan, Henderson, Farabow, et al.
700 Hansen Way
Palo Alto, CA 94304
Tel: (650) 849-6600
Fax: (650) 849-6666
Attorneys for Vysis, Inc.

John H. L'Estrange, Jr. Esq.
Wright and L'Estrange
701 B Street, Suite 1550
San Diego, CA 92101 4106 2118 3307
Tel: (619) 231-4844
Fax: (619) 231-6710

Executed on May 31, 2001, at San Diego, California.

Liz Hoke

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

vs.

VYSIS, INC.,

Defendant.

CASE NO. 99-CV-2668 H (AJB)

Order Granting Application for Expedited Briefing on Vysis' Motion for Entry of Final Judgment Under Rule 54(b)

On July 2, 2001, Vysis filed a Motion for Entry of Final Judgment Under Rule 54(b). Vysis seeks expedited briefing and hearing on the motion due to the discovery closure dates in the case. The Court GRANTS Vysis' request for an expedited briefing schedule. The Motion for Entry of Final Judgment is submitted on the papers pursuant to Local Rule 7.1(d.1).

IT IS SO ORDERED.

DATED: 7-11-01

Marilyn L. Huff

MARILYN L. HUFF, Chief Judge
UNITED STATES DISTRICT COURT

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99CV2668

Copies to:

Stephen Swinton
Cooley Godward LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121

Charles Lipsey
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1300 I Street, N.W., Suite 700
Washington, D.C. 20005

ORIGINAL

FILED

01 JUL 13 PM 2:23

CLERK, U.S. DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

BY: DEPUTY

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Attorneys for Defendant VYSIS, INC.

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

VYSIS' REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

Date: July 30, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

I. Entry of Judgment Under Rule 54(b) Will Expedite Final Resolution of Gen-Probe's Obligation to Pay Royalties

Gen-Probe's opposition is predicated primarily on an asserted desire for a rapid, final judicial determination of its obligation to pay royalties under the '338 patent license agreement with Vysis. Yet, the fastest way to secure such a resolution is to enter final judgment under Rule 54(b), Fed. R. Civ. P., on the infringement issue (Count I of the Second Amended Complaint) so that immediate appellate review may be had of this Court's construction of the '338 patent claims. That construction, if ultimately affirmed, is dispositive of Gen-Probe's obligation to pay royalties. If the claim construction urged upon this Court by Gen-Probe is correct, then every day that Gen-Probe delays appellate review of that determination is an added day that Gen-Probe must wait for ultimate judicial resolution of its royalty obligation.

More significantly, the claim construction ruling is also central to proper discovery and trial of the patent validity issues Gen-Probe now says it also wants to try. Gen-Probe has already limited its discovery responses based on the Court's narrow construction of the '338 patent, which will require additional discovery and trial if that claim construction is reversed (see Section III.A., *infra*). Indeed, if Vysis were to prevail on the issue of the validity of the '338 patent claims as narrowly construed by the Court, Gen-Probe would insist on retrying the validity issue if the claims are construed more broadly (as Vysis contends they should be) on appeal. Thus, the high likelihood is that, if the claim construction Gen-Probe has urged upon the Court is wrong, all of the discovery and trial activity undertaken in this Court in reliance on that claim construction would have to be redone, which would undoubtedly be followed by yet a second appeal.

Preparation of this case for trial, the trial itself, and resolution of post-trial motions in this case could not realistically be completed in less than nine months. That nine months of work will either be unnecessary if Gen-Probe's claim construction is correct or wasted if Gen-Probe's claim

construction is incorrect. Either way, delaying appeal of the infringement issue will *delay* ultimate judicial resolution of Gen-Probe's royalty obligations by at least nine months.[1]

II. Gen-Probe Has Misstated the Law Concerning Rule 54(b)

Gen-Probe's opposition brief misstates and misapplies the law relating to entry of final judgment under Rule 54(b). Contrary to Gen-Probe's suggestion, Vysis need not establish the existence of any "serious or irreparable consequences" to justify its Rule 54(b) motion. Gen-Probe's opposition asserts that

> The Federal Circuit has made clear that a trial court should deny a request for certification under Rule 54(b) where the moving party "has failed to disclose any 'serious, perhaps irreparable, consequence' flowing from the partial summary judgment and denial of [it's {sic}] Rule 54(b) motion." *Chaparral Communications, Inc. v. Boman Indus., Inc.*, 798 F.2d 456 (1986) *quoting Carson v. American Brands, Inc.*, 450 U.S. 79, 84 (1981).

Gen-Probe Opposition ("G-P Opp.") at 4.

That statement is flatly wrong. The Federal Circuit made no such pronouncement with respect to Rule 54(b) in the *Chaparral* case. In *Chaparral*, the district court had granted partial summary judgment against the appellant and denied its motion for entry of final judgment under Rule 54(b). The appellant then sought an appeal of that interlocutory decision to the Federal Circuit under 28 U.S.C. § 1292(a), arguing that the district court's grant of partial summary judgment against it had the effect of denying its request for injunctive relief. *Chaparral*, 798 F.2d 456, 457. It was in the context of determining the showing needed to take an interlocutory appeal under § 1292(a)(1), which by definition did *not* involve final disposition of an entire claim, that the Federal Circuit referred to the appellee's failure to disclose a "serious, perhaps irreparable, consequence" flowing from the district court's rulings. *Id.* at 458. *Chaparral* addressed the showing required for taking interlocutory appeals under *§ 1292(a)* – and most certainly did *not* address any standard

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[1] Gen-Probe overestimates the amount of time an appeal to the Federal Circuit would require. This case presents a pure question of law based on an abbreviated written record and not a series of complex, disputed factual issues resolved following trial on the merits. A more realistic estimate for resolution of this case is twelve months. *See AFG Indus., Inc. v. Cardinal IG Co.*, 239 F.3d 1239 (continued...)

required for granting motions for entry of final judgment under Rule 54(b). *Accord Woodard v. Sage Prods., Inc*, 818 F.2d 841, 855 (Fed. Cir. 1987) (en banc) (explaining holding of *Chaparral*).

Gen-Probe's reliance on *Sure-Safe v. C&R Pier Mfg.*, 851 F.2d 1469 (S.D. Cal. 1993), and *Lockwood v. American Airlines*, 1993 U.S. Dist. LEXIS 19768 (S.D. Cal. 1993), is misplaced for the same reason. In denying a motion for entry of final judgment under Rule 54(b), the trial court in *Sure-Safe* misread *Chaparral* in the same way Gen-Probe has, quoting the same "serious, perhaps irreparable, consequence" language. Thus, denial of the Rule 54(b) motion in *Sure-Safe* was based on the wrong legal standard. The *Lockwood* opinion issued by the same court just six weeks later was also undoubtedly affected by this improper standard.

Not only does Gen-Probe misapply the Federal Circuit *Chaparral* case, it also cites language from a Ninth Circuit case that has been subsequently rejected.[2] Gen-Probe cites *Morrison-Knudsen Co. v. J.D. Archer*, 655 F.2d 962, 965 (9th Cir. 1981), for the proposition that judgments under Rule 54(b) must be reserved for the "unusual case." Yet, *Morrison-Knudsen* has been repudiated by a subsequent Ninth Circuit panel as "an outdated and overly restrictive view of the appropriateness of Rule 54(b) certification." *Texaco, Inc. v. Ponsoldt*, 939 F.2d 794, 798 (9th Cir. 1991). In this regard, the trial court in *Lockwood* apparently also relied on the repudiated language of the *Morrison-Knudsen* case in holding that the movant had not made a showing that his case was "unusual." The *Lockwood* court cited *Frank Briscoe Co. v. Morrison-Knudsen Co.*, 776 F.2d 1414, 1416 (9th Cir. 1985), in support of the proposition that Rule 54(b) must be reserved for the "unusual case." *Lockwood*, 1993 U.S. Dist. LEXIS 19768 at *2. *Frank Briscoe*, in turn, adopted its "unusual case"

(...continued)
(Fed. Cir. Feb. 6, 2001) (vacating Feb. 25, 2000 district court summary judgment of noninfringement because of error in claim construction).

[2] Gen-Probe asserts that Ninth Circuit precedent controls here (G-P Opp. at 4 n.4), but the proper choice of law is unclear. *See W.L. Gore & Assocs., Inc. v. Int'l Medical Prosthetics Research Assocs., Inc.*, 975 F.2d 858, 860-61 (Fed. Cir. 1992) (affirming district court's entry of judgment under Rule 54(b) but declining to resolve question of which circuit's law governs the Rule 54(b) issue, and noting that "the Supreme Court has provided adequate guidance to resolve the issues presented . . . . To the extent Supreme Court precedent does not address each subissue and where neither Ninth Circuit nor Federal Circuit case law provides any guidance, we look to the law of all circuits equally for persuasive reasoning.").

language from the Ninth Circuit's 1981 *Morrison-Knudsen* case – the same case that was later repudiated by *Texaco*.

The Supreme Court has also rejected the notion that entry of judgment under Rule 54(b) can only be granted in the "infrequent harsh case." *Curtiss-Wright Corp. v. General Elec. Co.*, 446 U.S. 1, 10. In addition, *Angoss II Partnership v. Trifox, Inc.*, 2000 WL 288435 (N.D. Cal. 2000), a case cited in Gen-Probe's opposition, rejects the notion that a showing of substantial hardship is required to justify a Rule 54(b) judgment.

As discussed in Vysis' opening memorandum, entry of final judgment under Rule 54(b) is appropriate where there is no just reason for delay. *Texaco* indicates that Rule 54(b) certification is proper if it will aid "expeditious decision" of the case. 939 F.2d at 797. As shown in detail both here and in Vysis' opening memorandum, immediate appeal of this Court's claim construction to the Federal Circuit will result in the most expeditious resolution of the case. Indeed, even if a showing of unusual or serious consequences were required to justify entry of judgment under Rule 54(b), the burden Gen-Probe would impose upon Vysis and this Court to engage in nine months of unnecessary or wasted district court litigation certainly meets that standard.

III. The Court's Summary Judgment is Dispositive of Count I

Gen-Probe acknowledges that its Count I for non-infringement will be finally adjudicated if Vysis concedes non-infringement under the doctrine of equivalents.[3] To assure that the Court's summary judgment order is dispositive of Count I, Vysis hereby stipulates that, if the Court enters final judgment under Rule 54(b), it will not (and could not because it would be barred by that final judgment) assert that Gen-Probe's HIV/HCV test infringes the existing claims of the '338 patent under the doctrine of equivalents unless the trial court's construction is reversed, altered, or modified. Should the Federal Circuit affirm the Court's claim construction, Vysis will not later

[3] The parties apparently disagree over whether the Court's summary judgment ruling is dispositive of Count III of Gen-Probe's Second Amended Complaint. Because final adjudication of one count is sufficient for entry of final judgment pursuant to Rule 54(b), Vysis will not further address the finality of Count III in this memorandum, other than to reiterate its belief that the Court's summary judgment motion necessarily resolves the issues raised in that Count.

assert that Gen-Probe's HIV/HCV test kits infringe the existing claims of the '338 patent under the doctrine of equivalents.[4] Accordingly, Vysis' concession avoids the difficulties posed by the "uncertain" concession noted by Gen-Probe and criticized by the Federal Circuit in *CAE Screenplates Inc. v. Heinrichfielder GmbH & Co.*, 224 F.3d 1308, 1315 (Fed. Cir. 2000), in which the party seeking appeal "explicitly reserved its right to challenge infringement in the future should [the Federal Circuit] affirm the district court's construction." *Id.*

IV. There is No Reason to Proceed with Litigating Gen-Probe's Remaining Counts

A. Claim Construction Affects All Aspects of This Case

In its opposition memorandum, Gen-Probe asserts that its anticipation and obviousness theories do not depend on the Court's summary judgment determination. (G-P Opp. at 8.) That statement is simply wrong. As discussed in Vysis' opening memorandum, questions of anticipation and obviousness must be resolved with reference to the *claimed* invention, and the claims of the '338 patent must be properly construed before anticipation or obviousness can be determined.[5] Moreover, Gen-Probe has already indicated that it will use the Court's narrow claim construction to limit its responses to Vysis' discovery requests. In recent responses to Vysis' interrogatories, Gen-Probe objected to those interrogatories as seeking "information that is not relevant to the subject matter of this lawsuit" in view of the Court's summary judgment of noninfringement and its claim construction. See Gen-Probe's Objection and Response to Vysis' Interrogatory No. 10 (Exhibit ("Ex.") A to the Declaration of Thomas W. Banks in Support of Vysis' Reply Memorandum ("Banks Decl.").

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[4] Should this Court deny Vysis' motion for Rule 54(b) final judgment, however, Vysis reserves the right to proceed with a doctrine of equivalents theory during later proceedings on the infringement count.

[5] Gen-Probe also asserts that its nonenablement theory under 35 U.S.C. § 112 is independent of the Court's claim construction. (G-P Opp. at 8.) Yet in that very sentence, Gen-Probe states that "the '338 patent is invalid by reason of the inventors' failure to 'enable' the practice of the *claimed* invention as required by 35 U.S.C. § 112." *Id.* (emphasis added). Clearly, proper construction of the claims is a necessary predicate for resolving that issue, just as it is for resolving anticipation and obviousness. Moreover, resolution of Gen-Probe's unfair competition count also depends on proper (continued...)

Because the Court's claim construction is the foundation upon which all of the remaining issues of the case will rest, it is imperative that the claims be properly construed before addressing those issues. Any holding as to anticipation, obviousness, or nonenablement based on an incorrect construction of the claims of the '338 patent would require the parties to relitigate the case. Immediate appellate review by the Federal Circuit would avoid this serious risk. Thus, as discussed above and in Vysis' opening memorandum, it would be ill-advised to proceed with trial of the remaining issues absent appellate review of the fundamental issue of claim construction.

B. Proceeding to Try the Remaining Counts Will Not Alter Gen-Probe's Obligation To Pay Royalties

Gen-Probe's concern that it may continue to pay royalties pending final judicial resolution of the liability issues will not be addressed by refusing to permit immediate appeal of the infringement issue. Gen-Probe is free to cease paying royalties any time it wishes. If it chooses to continue to pay royalties following the summary judgment order it has elicited from this Court, it can only be due to a lack of certainty that that order can be sustained on appeal. Insisting that the parties proceed to trial on the possibly moot validity and enforceability issues cannot relieve Gen-Probe of that uncertainty. Even after trial, Gen-Probe would still face the uncertainty that any judgment it secures in its favor may be reversed on appeal. It is for this reason that the license agreement between the parties specifically contemplates the prospect of royalties until there is a final, unappealable judicial decision on the liability issue. See, e.g., Banks Decl. Ex. B, ¶ 1.3 (requiring exhaustion of all appeals). As noted above, the fastest way to secure that final judicial decision is to permit Vysis to appeal the infringement ruling immediately.[6]

(...continued)
claim construction because that count is based upon Gen-Probe's contention that the '338 patent is invalid and unenforceable.

[6] The only remaining relief sought by Gen-Probe – a questionable unfair competition claim for return of royalties paid – cannot be fully resolved against Vysis until there is a final decision on the liability issues, which is most expeditiously obtained by permitting an immediate appeal. Gen-Probe's claim to recover royalties paid can be resolved (if not dropped or settled) after the basic liability issue has been resolved.

C. The Court is Not Obligated to Try the Validity Issues

Gen-Probe's protestations concerning the need to resolve the validity of the '338 patent ring hollow. As discussed above, if the Federal Circuit affirms this Court's claim construction, the validity or enforceability of the '338 patent will have no bearing on Gen-Probe's obligations under the '338 license.

Though Gen-Probe suggests that the Court is required to address the validity issues it has raised, it is well settled that it is within the Court's discretion to refrain from deciding validity issues after it has made a finding of noninfringement. *See, e.g., Phonometrics, Inc. v. Northern Telecom Inc.*, 133 F.3d 1459, 1468 (Fed. Cir. 1998) (upholding district court's dismissal as moot of a counterclaim of invalidity and unenforceability in light of its grant of summary judgment of noninfringement and noting that "The Supreme Court's decision in *Cardinal Chemical Co. v. Morton International* [508 U.S. 83 (1993)] does not preclude this discretionary action by the district court"); *Child Craft Industries Inc. v. Simmons Juvenile Prods. Co.*, 990 F. Supp. 638 (S.D. Ind. 1998) ("the Court grants Plaintiff's request for declaratory judgment of noninfringement, [and] denies as moot Plaintiff's claim of invalidity of the patent"); *Signtech USA Ltd. v. Vutek Inc.*, 44 U.S.P.Q.2d 1741, 1747 (W.D. Tex. 1997) ("Having found that plaintiff has failed to show that either of defendant's devices infringe . . . , it is unnecessary to consider the invalidity and unenforceability arguments advanced by defendant."); *accord Durel Corp. v. Osram Sylvania Inc.*, 2001 U.S. App. LEXIS 14275, *25 (Fed. Cir. June 27, 2001) (refusing to remand case to district court for consideration of validity after affirming holding of noninfringement, noting that "Remand to consider the validity of a patent that we have held not to be infringed would be a poor use of judicial resources.").

Though Vysis has already identified the faulty legal bases of the decisions in *Sure-Safe* and *Lockwood*, those decisions also were based on an erroneous interpretation of Supreme Court precedent. Both *Sure-Safe* and *Lockwood* were rendered within a few months after the Supreme Court's *Cardinal Chemical* opinion was issued, and that opinion apparently heavily influenced the court's decision to try the validity issues even though it had already ruled that the defendants did not infringe the plaintiff's patents. *See Lockwood*, 1993 U.S. Dist. LEXIS 19768 at *3-4 (citing *Cardinal Chemical* as "effectively disposing" of plaintiff's arguments for Rule 54(b) certification);

Sure-Safe Indus., Inc. v. C&R Pier Mfg., 832 F. Supp. 293, 294 (S.D. Cal. 1993) (identifying *Cardinal Chemical* as the basis for ruling on validity issues). The court apparently viewed *Cardinal Chemical* as controlling, and on that basis proceeded to consider the validity issues of those cases. As discussed above, however, the more recent view of the Federal Circuit as well as various district courts is that *Cardinal Chemical* does *not* require trial of validity issues whenever noninfringement has been determined. Indeed, other courts have properly understood *Cardinal Chemical* as only preventing the Federal Circuit from vacating *existing* district court holdings of invalidity simply because a concurrent finding of noninfringement was affirmed. *See Phonometrics,* 133 F.3d 1459, 1468 ("*Cardinal Chemical* simply prohibits us, as an intermediate appellate court, from vacating a judgment of invalidity when we conclude that a patent has not been infringed, and therefore has no bearing on the district court's actions in this case.").

V. Conclusion

Vysis' motion is a plea for a common-sense approach to concluding this litigation. If we must try a series of complex patent validity and enforceability issues, let us try only those issues that truly need to be tried and let us try them only once!

Nothing in Gen-Probe's opposition blunts the logical force of that request. Indeed, it is the compelling logic of this procedure that leads trial courts routinely to grant entry of final judgment pursuant to Rule 54(b) in patent cases. *See, e.g., Bernard Dalsin Mfg. v. RMR Prods., Inc.*, 2001 U.S. App. LEXIS 8888 (Fed. Cir. May 7, 2001) (noting that after granting summary judgment of noninfringement, district court entered final judgment under Rule 54(b) and stayed further proceedings pending appeal);[7] *Desper Prods., Inc. v. QSound Labs, Inc.*, 157 F.3d 1325 (Fed. Cir. 1998) (noting that district court entered final judgment under Rule 54(b) after granting summary judgment of noninfringement); *Dethmers Mfg. Co. v. Automatic Equipment Mfg. Co.*, 189 F.R.D.

[7] Vysis cites this nonprecedential Federal Circuit opinion only for its historical report of the district court's actions in an apparently unpublished order, and not as appellate precedent.

526 (N.D. Iowa 1999) (entering judgment under Rule 54(b) after granting summary judgment on patent issues); *Dap Prods., Inc. v. Sashco, Inc.*, 1996 U.S. Dist. LEXIS 22529 (S.D. Ohio 1996) (entering judgment under Rule 54(b) on issue of infringement); *Dixie USA Inc. v. Infab Corp.*, 16 U.S.P.Q.2d 1392 (C.D. Cal. 1990), *aff'd* 927 F.2d 584 (Fed. Cir. 1991) (entering judgment under Rule 54(b) after granting summary judgment of noninfringement); *Allen-Bradley Co. v. Autotech Corp.*, 1989 U.S. Dist. LEXIS 6621 (N.D. Ill. 1989) (entering judgment under Rule 54(b) after granting summary judgment of infringement).

Accordingly, for the reasons set forth above and in Vysis' opening brief, Vysis' motion should be granted.

Dated: July 13, 2001

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ORIGINAL

FILED

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CLERK, U.S. DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

BY: DEPUTY

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

Case No.: 99CV 2668H (AJB)

CERTIFICATE OF SERVICE

CERTIFICATE OF SERVICE

I, the undersigned, declare under penalty of perjury that I am over the age of eighteen years and not a party to this action; my business address is 4665 Park Blvd., San Diego, California 92116; and that I served the below-named persons the following documents:

VYSIS' REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

DECLARATION OF THOMAS W. BANKS IN SUPPORT OF VYSIS' REPLY MEMORANDUM IN SUPPORT OF VYSIS' REPLY MEMORANDUM IN SUPPORT OF ITS MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

NOTICE OF LODGMENT OF CASE AUTHORITY NOT IN OFFICIAL REPORTER SYSTEM IN SUPPORT OF VYSIS' REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54 (b)

in the following manner:

1. X By personally delivering copies to the person served.

2. _____ By leaving, during usual office hours, copies in the office of the person served with the person who apparently was in charge and thereafter mailing (by first-class mail, postage prepaid) copies to the person served at the place where the copies were left.

3. _____ By leaving copies at the dwelling house, usual place of abode, or usual place of business of the person served in the presence of a competent member of the household or a person apparently in charge of his office or place of business, at least 18 years of age, who was informed of the general nature of the papers, and thereafter mailing (by first-class mail, postage prepaid) copies to the person served at the place where the copies were left.

4. _____ By placing a copy in a separate envelope, with postage fully prepaid, for each address named below and depositing each in the U.S. Mail at San Diego California on July 13, 2001.

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Executed on July 13, 2001, at San Diego, California.

DIVERSIFIED LEGAL SERVICES, INC.

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Attorneys for Defendant VYSIS, INC.

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

DECLARATION OF THOMAS W. BANKS IN SUPPORT OF VYSIS' REPLY MEMORANDUM IN SUPPORT OF ITS MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

Date: July 30, 2001
Time: 10:30 a.m.
Dept. Courtroom 1

I, Thomas W. Banks, declare and state as follows:

1. I have personal knowledge of the facts set forth in this declaration.

2. I am an attorney licensed to practice in the State of California and admitted to practice in the United States District Court for the Southern District of California. I am a partner at

the law firm of Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., and represent Defendant Vysis, Inc. ("Vysis") in this litigation.

3. Attached as Exhibit A to this declaration is a true and correct copy of Gen-Probe Incorporated's Objections and Responses to Vysis, Inc.'s Third Set of Interrogatories, Nos. 10 and 11.

4. Attached as Exhibit B to this declaration is a true and correct redacted copy of the Nonexclusive License Agreement Under Vysis' Collins Patents.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge and belief.

Executed this 12th day of July, 2001 at Palo Alto, California.

Thomas W. Banks

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Attorneys for Plaintiff
Gen-Probe Incorporated

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC., Defendant.	No. 99cv2668 H (AJB) **GEN-PROBE INCORPORATED'S OBJECTIONS AND RESPONSES TO VYSIS, INC.'S THIRD SET OF INTERROGATORIES, NOS. 10 & 11**

PROPOUNDING PARTY: **DEFENDANT VYSIS, INC.**

RESPONDING PARTY: **PLAINTIFF GEN-PROBE INCORPORATED**

SET NUMBER: **THREE (3)**

Pursuant to Federal Rule of Civil Procedure 33, Plaintiff Gen-Probe Incorporated ("Gen-Probe") responds as follows to Defendant Vysis, Inc.'s ("defendant") third set of interrogatories Nos. 10 and 11:

I. GENERAL RESPONSES.

1. Gen-Probe's response to defendant's third set of interrogatories is made to the best of Gen-Probe's present knowledge, information, and belief. Said response is at all times subject to such additional or different information that discovery or further investigation may disclose and, while based on the present state of Gen-Probe's recollection, is subject to such refreshing of recollection, and such additional knowledge of facts, as may result from Gen-Probe's further discovery or investigation. Gen-Probe reserves the right to make any use of, or to introduce at any hearing and at trial, information and/or documents responsive to defendant's first set of interrogatories but discovered subsequent to the date of this response, including, but not limited to, any such information or documents obtained in discovery herein.

2. To the extent that Gen-Probe responds to defendant's interrogatories by stating that Gen-Probe will provide information and/or documents which Gen-Probe, any other party to this litigation, or any other person or entity deems to embody material that is private, business confidential, proprietary, trade secret, or otherwise protected from disclosure pursuant to Federal Rule of Civil Procedure 26(c)(7), Federal Rule of Evidence 501, California Evidence Code section 1060, or California Constitution, article I, section 1, or any like or similar provision of law of any jurisdiction Gen-Probe will do so only upon the entry of an appropriate protective order against the unauthorized use or disclosure of such information.

3. Gen-Probe reserves all objections or other questions as to the competency, relevance, materiality, privilege or admissibility as evidence in any subsequent proceeding in or trial of this or any other action for any purpose whatsoever of Gen-Probe's responses herein and any document or thing identified or provided in response to defendant's interrogatories.

4. Gen-Probe reserves the right to object on any ground at any time to such other or supplemental interrogatories as defendant may at any time propound involving or relating to the subject matter of these interrogatories.

II. GENERAL OBJECTIONS.

1. Gen-Probe makes the following general objections, whether or not separately set forth in response to each interrogatory, to each instruction, definition, and interrogatory made in

defendant's first set of interrogatories:

2. Gen-Probe objects generally to interrogatories 10 and 11, insofar as they seek information or production of documents protected by the attorney-client or the attorney work product privilege. Such information or documents shall not be provided in response to defendant's interrogatories and any inadvertent disclosure or production thereof shall not be deemed a waiver of any privilege with respect to such information or documents or of any work product immunity, which may attach thereto.

3. Gen-Probe objects generally to each interrogatory to the extent it seeks to require Gen-Probe to identify in this response each or any document or other information which may relate to, reflect or otherwise refer to specified matters on the ground that such requests collectively encompass potentially thousands of pages of documents not all of which have or can be located and reviewed by counsel within the time period allowed by statute for this response. Accordingly, said request would subject Gen-Probe to unreasonable and undue annoyance, oppression, burden, and expense.

4. Gen-Probe objects to Definition B to the extent it defines "Gen-Probe" to include Gen-Probe's predecessors or successors; past or present divisions, subsidiaries, parents, or affiliates of any of the foregoing entities; past or present joint ventures, partnerships, or limited partnerships of which any of the foregoing entities is a joint venturer or a limited or general partner; and past or present directors, officers, employees, agents, or representatives of any of the foregoing entities. Said definition is vague and ambiguous in that it cannot be determined what is meant by the term "Gen-Probe." Said definition is also overly broad, seeks irrelevant information not calculated to lead to the discovery of admissible evidence, and would subject Gen-Probe and the other entities identified in the definition to unreasonable and undue annoyance, oppression, burden and expense.

5. Gen-Probe objects to the introductory statement to the extent it suggests that the interrogatories are continuing, on the ground that said instruction seeks unilaterally to impose an obligation to provide supplemental information greater than that required by Federal Rule of Civil Procedure 26(e) and would subject it to unreasonable and undue annoyance, oppression, burden, and expense. Gen-Probe will comply with the requirements of the Federal Rules of Civil

Procedure and is willing to discuss mutually acceptable reciprocal obligations of defendant for continuing discovery.

6. Gen-Probe objects to Instruction A to the extent it seeks to require Gen-Probe to identify anything other than the specific claim or privilege or work product being made and the basis for such claim, on the ground that the additional information sought by defendant would subject Gen-Probe to unreasonable and undue annoyance, oppression, burden, and expense, and constitutes information protected from discovery by privilege and as work product.

III. SPECIFIC OBJECTIONS AND RESPONSES TO INTERROGATORIES.

Without waiving or limiting in any manner any of the foregoing General Objections, but rather incorporating them into each of the following responses to the extent applicable, Gen-Probe responds to the specific interrogatories in defendant's first set of interrogatories as follows:

INTERROGATORY NO. 10:

State each factual and legal basis for Gen-Probe's contention that the form of target capture used by its nucleic acid tests for the detection of HIV and HCV in donated blood and blood products is not disclosed or claimed in the '338 patent, as set forth in Gen-Probe's response to Interrogatory No. 4.

RESPONSE TO INTERROGATORY NO. 10:

Gen-Probe incorporates into this response each of the foregoing General Responses and General Objections as if fully set forth herein. Gen-Probe objects to this interrogatory on the grounds that it seeks information that is not relevant to the subject matter of this lawsuit in view of the Court's June 20, 2001 "Order Granting Motion for Partial Summary Judgment of Non-Infringement of the '338 Patent; Claim Construction of the term "Amplifying" as found in the '338 Patent."

Subject to all of the foregoing, Gen-Probe states that it's method of target capture has been found to be patentably distinct from the prior art, including the '338 patent, by the U.S. Patent and Trademark Office (see U.S. Patent No. 6,110,678).

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INTERROGATORY NO. 11:

State whether Gen-Probe contends that its transcription mediated amplification (TMA) technique does not amplify the target polynucleotide as disclosed and claimed in the '338 Patent, and, if so, state each factual and legal basis for that contention.

RESPONSE TO INTERROGATORY NO. 11:

Gen-Probe incorporates into this response each of the foregoing General Responses and General Objections as if fully set forth herein. Gen-Probe objects to this interrogatory on the grounds that it seeks information that is not relevant to the subject matter of this lawsuit in view of the Court's June 20, 2001 "Order Granting Motion for Partial Summary Judgment of Non-Infringement of the '338 Patent; Claim Construction of the term "Amplifying" as found in the '338 Patent."

State whether Gen-Probe contends that its transcription mediated amplification (TMA) technique does not amplify the target polynucleotide as disclosed and claimed in the '338 Patent, and, if so, state each factual and legal basis for that contention.

Dated: June 29, 2001

COOLEY GODWARD LLP
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GEN-PROBE INCORPORATED
R. WILLIAM BOWEN, JR. (102178)

BROBECK PHLEGER & HARRISON LLP
DOUGLAS E. OLSON (38649)

By: _____
J. Christopher Jaczko

Attorneys for Plaintiff
Gen-Probe Incorporated

PROOF OF SERVICE
(FRCP 5)

I am a citizen of the United States and a resident of the State of California. I am employed in San Diego, State of California, in the office of a member of the bar of this Court, at whose direction the service was made. I am over the age of eighteen years, and not a party to the within action. My business address is 4365 Executive Drive, Suite 1100, San Diego, California 92121-2128. On the date set forth below I served the documents described below in the manner described below:

1. **GEN-PROBE INCORPORATED'S OBJECTIONS AND RESPONSES TO VYSIS, INC.'S THIRD SET OF INTERROGATORIES, NOS. 10 & 11**

☐ (BY U.S. MAIL) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of correspondence for mailing with the United States Postal Service, and I caused such envelope(s) with postage thereon fully prepaid to be placed in the United States Postal Service at Palo Alto, California.

☐ (BY MESSENGER SERVICE) by consigning the document(s) to an authorized courier and/or process server for hand delivery on this date. See attached Proof of Personal Service.

☑ (BY FACSIMILE) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of document(s) to be transmitted by facsimile and I caused such document(s) on this date to be transmitted by facsimile to the offices of addressee(s) at the numbers listed below. (No Exhibits Attached.)

☑ (BY OVERNIGHT MAIL) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of correspondence for overnight delivery, and I caused such document(s) described herein to be deposited for delivery to a facility regularly maintained by Federal Express for overnight delivery.

on the following part(ies) in this action:

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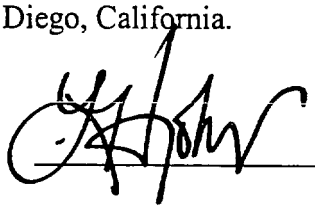
Executed on June 29, 2001, at San Diego, California.



Liz Hoke

NONEXCLUSIVE LICENSE
AGREEMENT UNDER VYSIS' COLLINS PATENTS

THIS NONEXCLUSIVE LICENSE AGREEMENT (the "AGREEMENT") is made and is effective the 22nd day of June, 1999 by and between Gen-Probe Incorporated ("GEN-PROBE"), a Delaware corporation having its principal place of business in San Diego, CA and Vysis, Inc. ("VYSIS"), a Delaware corporation having its principal place of business in Downers Grove, IL WITNESSETH:

RECITALS

WHEREAS, certain inventions generally characterized as Target and Background Capture Methods and Apparatus for Affinity Assays and Target and Background Capture Methods with Amplification for Affinity Assays are disclosed and claimed in United States Patents No. 5,780,224 and No. 5,750,338 by Collins and Collins, et al., respectively, and foreign counterparts thereto and other patents and applications claiming priority therefrom (the "Collins Patents");

WHEREAS, GEN-PROBE and VYSIS are engaged in litigation unrelated to VYSIS' Collins Patents and which litigation involves BP Amoco Corporation ("BP AMOCO"), an Indiana Corporation having its principal place of business in Chicago, IL;

REDACTED

GEN-PROBE and VYSIS agree hereto as follows:

1. DEFINITIONS

1.1 The term Collins Patents shall mean United States Patents No. 5,780,224, No. 5,750,338 and No. 5,457,025 by Collins, Collins, et al., and Collins et al. respectively, and foreign counterparts thereto, continuations, divisionals, reissues, and reexaminations thereof and other patents and applications claiming priority therefrom. A Schedule Of Collins Patents is attached as Exhibit 1 hereto and incorporated herein by reference.

1.2 The term Licensed Method shall mean any method, the use or practice of which would constitute, but for the license granted herein, an infringement of any issued, Valid Claim within the Collins Patents.

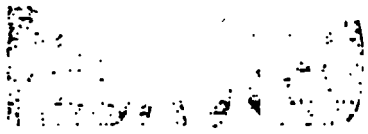
1.3 The term Valid Claim shall mean an issued claim of a Collins Patent which has not been ruled invalid by a court or an administrative agency of competent jurisdiction from which all appeals have been exhausted.

1.4 The term Licensed Product shall mean any of the following:

(a) Any product specifically intended for use in practicing a Licensed Method;

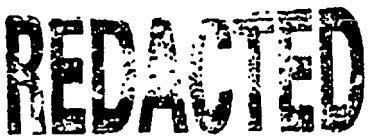
(b) Any product which lacks substantial use other than in practicing a Licensed Method; and

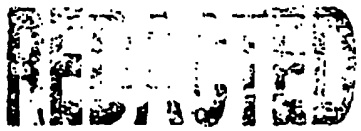
(c) Any product, the making, using, selling, offering for sale or importing of which, would constitute, but for the license granted herein, an infringement of any issued, Valid Claim within the Collins Patents.



2. GRANTS

2.1 Subject to the terms and conditions of this Agreement, VYSIS hereby grants to GEN-PROBE a worldwide, royalty-bearing, nonexclusive license without the right to sublicense, to make, use, sell, offer for sale, or import Licensed Products and practice Licensed Methods under the Collins Patents for use in the field of infectious disease nucleic acid testing.

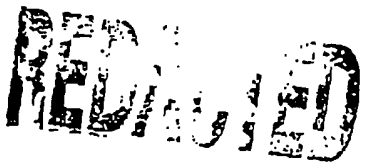




3. ROYALTIES AND PAYMENTS

3.1 GEN-PROBE agrees to make the following payments for the licenses received hereunder:

(b) A running royalty of percent of End User Net Commercial Sales of Licensed Products



REDACTED

REDACTED

4. TERM AND TERMINATION

1 Unless otherwise terminated by operation of law or by acts of the parties in accordance with
: terms of this Agreement, this Agreement shall be in force from June 22, 1999 and shall
main in effect for the life of the last-to-expire of the Collins Patents.

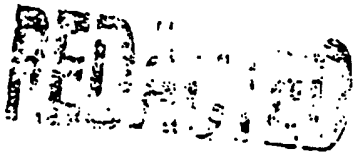
REDACTED

4.4 GEN-PROBE may terminate upon written notice of termination to VYSIS. Thereafter, the license and rights previously granted shall terminate automatically on the effective date of the Notice of Termination.

REDACTED

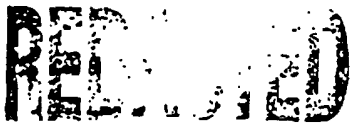
REDACTED

REDACTED



12. GOVERNING LAW

12.1 This Agreement is made in partial fulfillment of and reflects terms specified in a Definitive Agreement and Release entered into by the parties in settlement of litigation in the United States District Court for the Southern District of California in the matter Gen-Probe, Incorporated v. Amoco Corp., et al. (Case No. 95-CV-998-J(BTM)). The Agreement and its construction are subject to the laws of the state of California with the exception of any choice of law provisions which would direct the application of another state's laws. The Agreement and its construction are further subject to the continuing jurisdiction of the United States District Court for the Southern District of California.



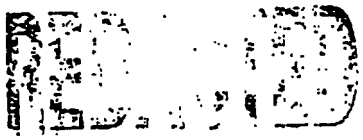
IN WITNESS WHEREOF VYSIS and GEN-PROBE have executed this Agreement, in duplicate originals, by their respective officers hereunto duly authorized, on the day and year written below.

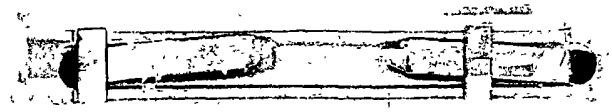
VYSIS, INC.	GEN-PROBE INCORPORATED
By: _____	By: _____
Title: _____	Title: President & Chief Exec. Officer
Date: _____	Date: August 10, 1999

APPROVED LEGAL

Schedule of Collins Patents*

REDACTED





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CLERK, U.S. DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

BY: DEPUTY

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Attorneys for Defendant VYSIS, INC.

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

NOTICE OF LODGMENT OF CASE AUTHORITY NOT IN OFFICIAL REPORTER SYSTEM IN SUPPORT OF VYSIS' REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF VYSIS' MOTION FOR ENTRY OF FINAL JUDGMENT UNDER RULE 54(b)

Date: July 30, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE that Defendant Vysis, Inc. hereby lodges the following cases which do not appear in the official Federal Reporter system, but which are cited in its Reply Memorandum Of Points And Authorities In Support Of Vysis' Motion For Entry Of Final Judgment Under Rule 54(b):

EXHIBIT 1: *Lockwood v. American Airlines,* 1993 U.S. Dist. LEXIS 19768 (S.D. Cal. 1993);

EXHIBIT 2: *Angoss II Partnership v. Trifox, Inc.,* 2000 WL 288435 (N.D. Cal. 2000);

EXHIBIT 3: *Signtech USA Ltd. v. Vutek Inc.,* 44 U.S.P.Q.2d 1741 (W.D. Tex. 1997);

EXHIBIT 4: *Durel Corp. v. Osram Sylvania Inc.,* 2001 U.S. App. LEXIS 14275 (Fed. Cir. June 27, 2001);

EXHIBIT 5: *Bernard Dalsin Mfg. v. RMR Prods., Inc.,* 2001 U.S. App. LEXIS 8888 (Fed. Cir. May 7, 2001);

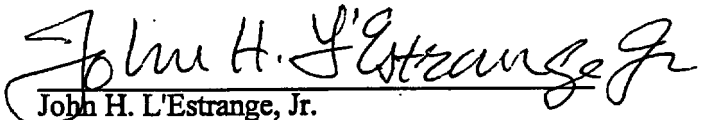
EXHIBIT 6: *Dap Prods., Inc. v. Sashco, Inc.,* 1996 U.S. Dist. LEXIS 22529 (S.D. Ohio 1996);

EXHIBIT 7: *Dixie USA Inc. v. Infab Corp.,* 16 U.S.P.Q.2d 1392 (C.D. Cal. 1990); and

EXHIBIT 8: *Allen-Bradley Co. v. Autotech Corp.,* 1989 U.S. Dist. LEXIS 6621 (N.D. Ill. 1989)

Date: July 13, 2001

WRIGHT & L'ESTRANGE



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LEXSEE 1993 us dist lexis 19768

LAWRENCE B. LOCKWOOD, Plaintiff v. AMERICAN AIRLINES, INC., Defendant.

Civil No. 91-1640-E(CM)

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF CALIFORNIA

1993 U.S. Dist. LEXIS 19768; 29 U.S.P.Q.2D (BNA) 1637

September 21, 1993, Decided

September 21, 1993, Filed

JUDGES:
[*1] ENRIGHT

OPINIONBY:
WILLIAM B. ENRIGHT

OPINION:

MEMORANDUM DECISION AND ORDER

BACKGROUND

On July 30, 1993, the court entered a Memorandum Decision and Order granting defendant's motion for summary judgment on non-infringement grounds. On August 6, 1993, the clerk's office inadvertently entered judgment in this case.

Plaintiff now moves this court to clarify any uncertainty surrounding the judgment entered by the clerk's office by entering a final judgment in this case pursuant to Rule 54(b) as to plaintiff's claim of patent infringement. In addition, plaintiff asks that the court expressly determine that there is no just reason for delaying an appeal from the final judgment. The patent infringement claim is the only claim asserted in the complaint.

Defendant has asserted counterclaims seeking attorneys' fees and a declaration that the patents in suit are invalid. It argues that the invalidity counterclaim is crucial to the continuing conduct of defendant's computer reservation business. Thus, it argues that the court should decide the validity issue, despite the non-infringement ruling, so that defendant has the possibility of becoming free from future litigation by Lockwood involving SABREvision. Defendant [*2] also argues that the court should deny plaintiff's motion because it is not likely to be successful and would unreasonably delay resolution of this case for more than a year.

DISCUSSION

Fed. R. Civ. P. 54(b) gives the court discretion to direct the entry of a final judgment as to one or more of the claims upon the express determination that there is no just reason for delay. Judgments under Rule 54(b) must be reserved for the unusual case in which the costs and risks of multiplying the number of proceedings and of overcrowding the appellate docket are outbalanced by pressing needs of the litigants for an early and separate judgment. *Frank Briscoe Co. v. Morrison-Knudsen Co., 776 F.2d 1414, 1416 (9th Cir. 1985).*

Lockwood argues that Rule 54(b) relief is warranted because the judgment: 1) finally determined plaintiff's claim; and 2) the infringement issue is separate from the other claims for relief. See *W.L. Gore v. Intern Medical Prosthetics Research, 975 F.2d 858 (Fed. Cir. 1992).*

Additionally, plaintiff argues that the most efficient course of action for this court is to enter a final judgment on the infringement [*3] issue. However, all of plaintiffs arguments are effectively disposed of by a recent decision by the Supreme Court. See *Cardinal Chemical Co. v. Morton International, Inc., 124 L. Ed. 2d 1, 113 S. Ct. 1967 (1993).*

First, plaintiff argues that the infringement issue finally determined plaintiff's claim. It cites Gore for the proposition that once the district court decides the infringement issue, it need not decide the invalidity issue. Id. However, the Supreme Court has recently

indicated its preference that district courts rule on both the invalidity and infringement issues, even when non-infringement is found. See *Cardinal Chemical Co. v. Morton International, Inc., 124 L. Ed. 2d 1, 113 S. Ct. 1967 (1993).*

Second, Lockwood argues that the infringement claim is separate from the validity issue because they involve different factual and legal issues. While this argument is technically true, it was given little consideration by the Supreme Court in Cardinal, where it indicated that district courts should decide both the infringement and validity questions. See Id.

Finally, Lockwood [*4] argues that it would be more efficient for this court to enter a final judgment and allow an immediate appeal because if the non-infringement ruling is upheld there will be no reason to try the validity issue. However, in Cardinal, the Supreme Court noted the importance to the public at large of deciding patent validity issues. See Id. Thus, even if the non-infringement ruling were upheld, this court would still need to address the validity issue.

This court agrees with defendant that Lockwood has presented no evidence or argument which suggests that this is an unusual case warranting relief under Rule 54(b). The arguments made by plaintiff are the same arguments that could be made in every patent case. In light of the direction provided by the Supreme Court in Cardinal Chemical, this court finds that granting plaintiff's Rule 54(b) motion would only unnecessarily delay resolution of this case. Thus, plaintiff's Rule 54(b) motion is denied and this case will continue in the normal course of events.

CONCLUSION

Upon due consideration of the parties' memoranda and exhibits, the arguments advanced at hearing, and for the reasons set forth above, the court hereby denies [*5] plaintiff's Rule 54(b) motion. The clerk's office is directed to vacate the judgment issued in this case.

DATED: September 21, 1993.

WILLIAM B. ENRIGHT, Judge

United States District Court

Only the Westlaw citation is currently available.

United States District Court, N.D. California.

ANGOSS II PARTNERSHIP, Angoss Software International (USA), Inc., and Angoss Software International, Ltd., Plaintiffs,
v.
TRIFOX, INC., Defendant.

No. C 98-1459 SI.

March 13, 2000.

ORDER CERTIFYING JUDGMENT IN FAVOR OF PLAINTIFF AS FINAL UNDER FEDERAL RULE OF CIVIL PROCEDURE 54(b)

JENKINS, J.

***1** This Court heard oral argument on this motion on March 10, 2000. Having carefully considered the papers submitted and the argument of the parties, the Court GRANTS plaintiffs' motion for certification of judgment pursuant to Federal Rule of Civil Procedure 54(b).

INTRODUCTION

1. Factual History

Plaintiffs filed suit in 1995 against defendant Trifox in Ontario, Canada alleging breach of contract. *See Angoss II Partnership, et. al. v. Trifox, Inc.,* Court File 95-CU-86750. Plaintiffs' claim arose from a contract under which plaintiffs agreed to purchase software products from the defendant. The suit alleged that defendant's products could not be utilized to build computer applications and that installation of the products was impossible. The trial on the Canadian breach of contract claim commenced in 1997. The Canadian court found in favor of plaintiffs in December 1997 and ordered the defendant to pay $4,918,065 (Canadian). *See* Def. Opposition to Rule 54(b) Motion, Ex. A. That decision also held that plaintiffs "have no right, title or interest of any nature or kind in [defendant's products]." *Id.* The defendant filed a notice of appeal of the judgment; on October 19, 1999 the appeal was denied.

2. Procedural History

On April 9, 1998, plaintiffs filed a complaint in the Northern District of California seeking recognition of the Canadian judgment by this Court. On July 21, 1998 the Court issued an order granting summary judgment on plaintiffs' claims. However, the Court simultaneously stayed enforcement of that order pending appeal of the Canadian judgment. On September 17, 1998, defendant filed counterclaims for copyright and trademark infringement founded upon alleged actions performed by plaintiffs after the entry of the Canadian judgment. On April 2, 1999 the Court stayed proceedings on defendant's counterclaims. On January 6, 2000, the Court lifted those stays for the sole purpose of filing the present Rule 54(b) motion.

LEGAL STANDARD

Under Federal Rule of Civil Procedure 54(b),

> [w]hen more than one claim for relief is presented in an action, ... or when multiple parties are involved, the court may direct entry of a final judgment as to one or more but fewer than all of the claims or parties only upon an express determination that there is no just reason for the delay ...

Fed.R.Civ.P. 54(b). A ruling is final, and therefore appealable "if it 'ends the litigation on the merits and leaves nothing for the court to do but execute the judgment' " as to that party or claim. *Arizona State Carpenters Pension Trust Fund v. Miller,* 938 F.2d 1038, 1039 (9th Cir.1991) (*quoting Gulfstream Aerospace Corp. v. Mayacamas Corp.,* 485 U.S. 271, 275 (1988)). "The Rule 54(b) claims do not have to be separate from and independent of the remaining claims." *Sheehan v. Atlanta Int'l Ins. Co.,* 812 F.2d 465, 468 (9th Cir.1987). Rule 54(b) certification is left to the sound discretion of the district court, and certification is proper if it aids in expeditious resolution of the case while avoiding piecemeal appeals. *See Core-Vent Corp. v. Nobel Indus. AB,* 11 F.3d 1482, 1484 (9th Cir.1993).

***2** Rule 54(b) was enacted to counter the "liberalization of our practice to allow more issues and parties to be joined in one action ." *Dickinson v. Petroleum Conversion Corp.,* 338 U.S. 507, 511 (1950). Accordingly, "the trend is towards greater deference to a district court's decision to certify under Rule 54(b)." *See Texaco, Inc. v. Ponsoldt,* 939 F.2d 794, 798 (9th Cir.1991) (citations omitted). In making its decision, a district court should adopt "a pragmatic approach focusing on severability and efficient judicial administration." *See Continental Airlines v. Goodyear Tire & Rubber Co.,* 819 F.2d 1519, 152 (9th Cir.1987).

DISCUSSION

In their motion, plaintiffs argue that there is no just reason to delay entry of judgment under Rule 54(b). They further assert that concerns of equity and judicial economy weigh in favor of granting such judgment. Defendant opposes this motion and contends that plaintiffs have not made a substantial showing to warrant the Rule 54(b) judgment. Defendant further asserts that equity will be served by denying a Rule 54(b) judgment because, *inter alia,* plaintiffs are responsible for the delays in this case.

In order to grant a Rule 54(b) motion, a court must first determine if Rule 54(b) is applicable to the proceedings. First, there must be an action involving multiple claims for relief. *See Liberty Mutual Ins. Co. v. Wetzel,* 424 U.S. 737, 96 S.Ct. 1202 (1976). Here, defendant's counterclaims satisfy this requirement. Second, there must be a final decision by the district court on at least one claim. *See Bank of Lincolnwood v. Federal Leasing, Inc.,* 622 F.2d 944, 947 (7th Cir.1980). The Court's July 21, 1998 summary judgment order is sufficient to fulfill this requirement. If a court finds these two factors present, the court must expressly determine that there is no just reason for the delay, and must expressly direct the entry of judgment. *See id.*

In determining whether there are just reasons for a delay, the district court "must take into account judicial administrative interests as well as equities involved." *See Curtiss-Wright Corp. v. General Electric Co.,* 446 U.S. 1, 8, 100 S.Ct. 1460, 1465 (1980). When considering judicial interests, the Court must determine "whether the claims under review [are] separable from the others remaining to be adjudicated and whether the nature of the claims already determined was such that no appellate court would have to decide the same issues more than once." *Id.* at 1465. Equitable factors considered by the Court include, but are not limited to, (1) the prejudgment interest rate, (2) the liquidity of the debts at issue, (3) the threat of either party becoming insolvent, (4) the possibility that counterclaims will create setoffs against the judgment. *See id.* at 1466-67. In *Curtiss-Wright,* the Court expressly rejected the rule that Rule 54(b) motions should be reserved for "the infrequent harsh case." *Id.* at 1465.

1. Judicial Economy

***3** Judicial economy calls for entry of final judgment on plaintiffs' claim. Plaintiffs' claim and defendant's counterclaims have few factual allegations in common. [FN2] Plaintiffs' claim arises out of a breach of a Canadian contract entered into in 1993, and contested in 1995. The alleged facts that give rise to defendant's counterclaim for trademark and copyright infringement did not occur until 1997. [FN3] Further, defendant's counterclaim alleges actions taken by plaintiffs in California, not Canada. This Court granted summary judgment solely on the Canadian decision in the breach of contract action.

FN2. In this Court's Order Granting Leave to File Counterclaims ("Order"), the Court held that "[t]he counterclaims defendant seeks to file are independent of the rights associated with contract ." Order at 3.

FN3. The Order further states, "the alleged infringement did not occur until after the Canadian court entered judgment." Order at 2.

Therefore, any facts that support summary judgment on the plaintiffs' claim are distinct in time and place from defendant's counterclaims. Because these facts are severable, judicial economy calls for entry of judgment pursuant to Rule 54(b). This analysis "depends not on whether there are any facts in common between the adjudicated and the unadjudicated claim, but rather whether the factual issues 'at the heart' of the claims are sufficiently distinct." *Prudential Ins. Co. v. Curt Bullock Builders, inc.,* 626 F.Supp. 159, 169 (D.Ill.1985); *see also W.L. Gore & Assoc. v. Int'l Medical Prosthetics Research Assoc., Inc.,* 975 F.2d 858, 864 (Fed.Cir.1992). Further, because defendant's counterclaim for trademark and copyright infringement arose out of completely separate facts, an appellate court would not have to review defendant's breach of contract more than once.

2. Equitable Concerns

"[T]he district court should feel free to consider any factor that seems relevant to a particular action, keeping in mind the policies the rule attempts to promote." *Bank of Lincolnwood,* 622 F.2d at 949. In this case, each party raises various equitable concerns which relate to the Rule 54(b) motion. At the outset, the Court concludes that there is no authority to support defendant's contention that a showing of substantial hardship is required to justify a Rule 54(b) judgment.

Defendant argues that plaintiffs have caused the delays in this case and, were it not for plaintiffs' own request for a stay, the present Rule 54(b) motion would be unnecessary. The Court does not agree. The cause for the current stay of plaintiffs' action is defendant's appeal of the Canadian court's judgment. Plaintiffs did file, and were granted, a stay on defendant's counterclaims. However, such a stay was reasonable given that plaintiffs' claim had been stayed per defendant's request. Both parties have contributed to the delays in this case. The defendant's attempt to place blame solely on the plaintiffs is incorrect.

Plaintiffs argue that by not certifying the judgment, their ability ultimately to collect is prejudiced. They further claim that defendant is in a precarious financial situation. This contention is supported by defendant's actions. Defendant claims that if judgment is entered, it may be forced into bankruptcy or rendered financially incapable of litigating its counterclaims. In *Bank of Lincolnwood,* the Seventh Circuit held that this fact "is more relevant to whether the trial court should stay enforcement of the judgment" and further held that this circumstance alone does not warrant denial of a Rule 54(b) motion. 622 F.2d at 949, n. 8. By its own admission, defendant's financial instability has forced defendant to reduce production and development of its products. *See* Decl. of Nicklas Back, § § 1, 5. Therefore, there is considerable merit in the plaintiffs' contention that any further delay in judgment might impair their ability to collect. There would be considerable prejudice to plaintiffs if entry of judgment were denied.

***4** Plaintiffs further argue that the debts at issue are considerably liquidated, which supports certification. The amount of the judgment was explicitly stated in the Canadian court's decision and that amount has been converted into American dollars. Canadian courts grant an automatic stay of enforcement pending the first appeal. However, the Canadian appellate court has rejected defendant's appeal, and the stay of judgment in Canada has been lifted. Therefore, the Court agrees with plaintiffs that the debts are liquidated, and thus ripe for payment.

A final equitable concern to be considered is the potential that success of defendant's counterclaims may create a setoff against plaintiffs' judgment. While this is not an insignificant factor, the possibility of a setoff is not substantial enough to reserve entry of judgment. *See* Curtiss-Wright, 100 S.Ct. at 1467. Additionally, the Court notes that the defendant argues that only a setoff might result from the counterclaims, as opposed to a complete dissolution of plaintiffs' judgment. Therefore, even if judgment were reserved until all claims were resolved, plaintiffs would still be entitled to collect from defendant. This weighs in favor of entering judgment due to the aforementioned prejudice. *See id.* Further, any setoff defendant might receive can be resolved separately if and when such judgment for defendant is entered. *See* Prudential Life Ins., 626 F.Supp. at 169.

CONCLUSION

Because judicial economy argues for certification, and because the balance of equitable factors supports entry of judgment, this Court GRANTS plaintiffs' motion for entry of final judgment under Rule 54(b), and certifies judgment of plaintiffs' claim in accordance with the summary judgment this court granted on July 21, 1998.

IT IS SO ORDERED.

END OF DOCUMENT

EXHIBIT 3

LEXSEE 44 uspq2d 1741

SIGNTECH USA, LTD., Plaintiff, v. VUTEK, INC., Defendant.

CIVIL ACTION NO. SA-95-CA-0226

UNITED STATES DISTRICT COURT FOR THE WESTERN DISTRICT OF TEXAS, SAN ANTONIO DIVISION

1997 U.S. Dist. LEXIS 20292; 44 U.S.P.Q.2D (BNA) 1741

September 30, 1997, Decided

September 30, 1997, Filed

DISPOSITION:
[*1] Defendant entitled to a basic damage award of $ 140,000 for infringement by plaintiff of the '522 patent, prejudgment interest in the amount of $ 28,818, plus enhanced damages of $ 420,000 for plaintiff's willful infringement of the '522 patent, a permanent injunction against plaintiff for any further infringement of the '522 patent, and attorney's fees.

COUNSEL:
For SIGNTECH USA, LTD, plaintiff: David J. Williams, Attorney at Law, San Antonio, TX.

For SIGNTECH USA, LTD, plaintiff: William D. Harris, Jr., Locke Purnell Rain Harrell, Dallas, TX.

For VUTEK, INC., defendant: Luke C. Kellogg, Perry & Kellogg, San Antonio, TX.

For VUTEK, INC., defendant: Alan D. Rosenthal, Howard L. Speight, FISH & RICHARDSON, P.C., Houston, TX.

For VUTEK, INC., defendant: John M. Skenyon, Jolynn Marie Lussier, FISH & RICHARDSON, P.C., Boston, MA.

For VUTEK, INC., counter-plaintiff: Luke C. Kellogg, Perry & Kellogg, San Antonio, TX.

For VUTEK, INC., counter-plaintiff: Alan D. Rosenthal, Howard L. Speight, FISH & RICHARDSON, P.C., Houston, TX.

For VUTEK, INC., counter-plaintiff: John M. Skenyon, Jolynn Marie Lussier, FISH & RICHARDSON, P.C., Boston, MA.

For SIGNTECH USA, LTD, counter-defendant: David J. Williams, Attorney at Law, San Antonio, TX.

For SIGNTECH USA, LTD, counter-defendant: William D. Harris, Jr., Locke Purnell Rain Harrell, Dallas, TX.

JUDGES:
NANCY STEIN NOWAK, United States Magistrate Judge.

OPINIONBY:
NANCY STEIN NOWAK

OPINION:

MEMORANDUM OPINION AND ORDER

This matter comes before the Court for entry of findings of fact and conclusions of law after trial, conducted with the consent of the parties to my jurisdiction pursuant to *28 U.S.C. § 636*(c).

Summary

This is a patent infringement case involving ink jet printers used for making large signs. Plaintiff sued defendant alleging Vutek Models 3200 and 3200i infringe plaintiff's U.S. Patent No. 5,376,957 ('957 patent) which claims an ink jet printer that prints large signs with identical images printed in registry on the front and reverse sides. Defendant denies infringement and further contends that the '957 patent is invalid and unenforceable due to plaintiff's inequitable conduct

before the Patent and [*2] Trademark Office, as well as for lack of enablement, failure to disclose the best mode, and obviousness.

Defendant counterclaimed for infringement of its U.S. Patent 4,914,522 ('522 patent), which covers an ink jet print head for making large signs by using pulse width modulation of the airflow to the ink jets. I have previously found and plaintiff has stipulated that Signtech's DH1600 printer infringes claims 12, 13 and 18 of this patent. In defense of the infringement finding, plaintiff contends that the '522 patent is invalid as obvious or as anticipated. Defendant seeks enhanced damages and attorney's fees alleging that the infringement was willful.

I. '957 Patent - Claims construction and infringement

Plaintiff has the burden to prove its claims of infringement by a preponderance of the evidence. n1 There are two separate legal theories of infringement. One is literal infringement. The other is infringement under the doctrine of equivalents. n2 Literal infringement is only proven if the accused device literally includes every element (or "limitation") of the patent claim. n3

n1 ***Lemelson v. United States***, *752 F.2d 1538, 1547 (Fed. Cir. 1985).* [*3]

n2 ***Atlas Powder Co. v. E.I. DuPont de Nemours***, *750 F.2d 1569, 1579 (Fed. Cir. 1984).*

n3 ***Mannesmann Demag Corp. v. Engineered Metal Prods. Co., Inc.***, *793 F.2d 1279, 1282 (Fed. Cir. 1986);* ***Carroll Touch Inc. v. Electro Mechanical Systems, Inc.***, *3 F.3d 404, 407 (Fed. Cir. 1993).*

The analysis of the infringement claim begins with interpreting the claims of the '957 patent, and then comparing those claims with the accused device. n4 To ascertain the meaning of claims, the Court should consider three sources: the claims, the specification, and the prosecution history. n5 Claims must be read in view of the specification, of which they are a part. the description contained in the specification "may act as a sort of dictionary, which explains the invention and may define terms used in the claims." n6 Similarly, the Court has broad power to look to the prosecution history -- the public record of proceedings in the Patent and Trademark Office -- "to ascertain the true meaning of language used in patent claims." n7 Expert testimony, including evidence of the state of the [*4] prior art and how those skilled in the art would interpret the claims, may also be used to assist the Court in understanding scientific or technical terms. n8

n4 ***Markman v. Westview Instruments, Inc.***, *52 F.3d 967, 976 (Fed. Cir. 1995)* (en banc), aff'd, *517 U.S. 370, 116 S. Ct. 1384, 134 L. Ed. 2d 577 (1996).*

n5 ***Id.***, *at 979.*

n6 **Id.**

n7 ***Id.***, *at 980.*

n8 **Id.**

Claim 1 of the '957 patent reads as follows:

1. An apparatus for reproducing an image on a first side of a substrate and a mirror image on a second side of said substrate, comprising:

a frame;

means for generating control signals representative of said image;

ink delivery means positioned on opposite sides of said substrate, said ink delivery means fluidly communicating with an ink source,

means mounted on said frame for supporting said ink delivery means;

means mounted on said frame for driving said ink delivery means relative to said substrate; and

means responsive to said [*5] control signals, for controlling said ink delivery means to produce said image on said first side of said substrate and said mirror image on said second side of said substrate.

(Plaintiff's Exhibit No. 1, col. 11, lines 29-45).

The "ink delivery means" of Claim 1 is referred to as a "means plus function" claim element, authorized by *35 U.S.C. § 112,* P6, which provides as follows:

An element in a claim for a combination may be expressed as a means or step for performing a specified function without recital of structure, material, or acts to support thereof, and such claim shall be construed to cover the corresponding structure, material or acts described in the specification and equivalents thereof.

(emphasis added). According to the second clause of P6, a "means plus function" claim must be interpreted to

cover the structure, material or acts described in the patent specification and its equivalents. n9 In order for a "means plus function" limitation to read on an accused device, the accused device must employ means identical to or the equivalent of the specific structures, material, or acts described in the patent specification itself for [*6] those "means". "The accused device must also perform the identical function as specified in the claims" (emphasis added). n10

n9 ***King Instruments Corp. v. Perego***, *65 F.3d 941, 945 (Fed. Cir. 1995),* **cert. denied.** *134 L. Ed. 2d 778, 116 S. Ct. 1675 (1996);* ***Laitram Corp. v. Rexnord, Inc.***, *939 F.2d 1533, 1536 (Fed. Cir. 1991);* ***Valmont Indus., Inc. v. Reinke Mfg. Co., Inc.***, *983 F.2d 1039, 1042 (Fed. Cir. 1993).*

n10 ***Valmont Indus., Inc. v. Reinke Mfg. Co., Inc.***, *983 F.2d 1039, 1042 (Fed. Cir. 1993).*

Turning to the '957 patent itself, the Abstract explains:

The present invention is further provided with dual air sources to apply the ink. A first source is pulse width modulated to control the amount of ink sprayed onto the substrate. A second air pressure source is continuously applied to the ink jet spray nozzles to remove the excess ink that accumulates about the nozzles during print operations.

(emphasis added). (Plaintiff's Exhibit [*7] No. 1).

The Background of the Invention section describes the prior art (specifically the '522 patent and the 4,999,651 patent, both held by Peter Duffield, a principal of Vutek) as "incapable of producing an image in one continuous print" resulting in "incorrect ink densities" because of problems of misting and accumulation of ink on the nozzles; in short, an image that falls short of the quality desired. n11 The Background of Invention concludes:

Accordingly, the ink jet printer system of the present invention implements a design which overcomes the problem of ink accumulation on the spray head nozzles. The present invention is provided with dual pressure sources, a low volume high pressure constant air source to prevent the accumulation of excess ink on the nozzles, and a high volume low pressure constant air source for drawing the ink from the nozzles for application to the imaging medium.

(Plaintiff's Exhibit 1, col. 2, line 56-64).

n11 Plaintiff's Exhibit 1, col. 2, lines 52-54.

The Summary [*8] of the Invention section of '957 also describes the problem of ink accumulation and poor print quality, and the solution provided through the ink delivery means of the present invention.

First, the present invention is capable of producing a sectioned image on the substrate in one continuous print because its sprayhead design prevents ink jet clogging. The sprayheads of the present invention are connected to two separate air pressure sources which operate to apply the ink and prevent the ink jets from becoming clogged. A low pressure, high volume air source is pulse width modulated as described above to apply the ink onto the substrate to the density desired for the reproduced pixel. A second high pressure, low volume, air source continuously communicates with the ink jets to prevent ink build-up. The prevention of ink build-up by the second high pressure air source produces dual results. With no ink build-up, the ink jets first do not clog, and second, do not produce incorrect colors on the substrate. Color variations occur because the excess ink about the ink jets changes the effective dimensions of the spray means, thus changing the air and ink flow rates resulting [*9] in either a change in the color itself or a change in the particular shade of the color applied to the substrate. Thus, the utilization of the second air source makes the present invention a significant improvement over conventional ink jet printer systems.

(emphasis added). (Plaintiff's Exhibit 1, col. 3, lines 25-48).

In describing the preferred embodiment shown in figure 5 n12 in narrative, the specification states:

Referring to FIG. 5, the configuration and operation of the individual ink jets will be described. For the purpose of disclosure, ink spray head 23A will be described because each of sprayheads 23A-D and 25A-D operate similarly. Ink spray head 23A comprises ink reservoir 31A which fluidly communicates with ink jet 32. Ink reservoir 31A operates under a gravity siphon feed system to supply ink to the tip of ink jet 32 creating a meniscus. Ink sprayhead 23A further communicates with a high pressure compressed air source (not shown) and a low pressure compressed air source (not shown).

The high pressure compressed air source is continually in communication with ink jet nozzle 32 through passage 33 to supply an air flow around nozzle 32. That continuous air [*10] flow operates to prevent

ink build-up on nozzle 32 resulting in a color change during continuous operation.

(emphasis added). (Plaintiff's Exhibit 1, col. 7, lines 35-51). As shown, the specification consistently describes the ink delivery means and the production of a good quality print as requiring the second high pressure air source.

n12 Figure 5 of the '957 patent:

[SEE Fig. 5 IN ORIGINAL]

Plaintiff argues that the second high pressure air source performs a cleaning function and therefore cannot be part of the ink delivery means. However, as a "means plus function" element I am instructed by the applicable law to construe the claim in the context of the structure in which it operates and the function it performs. By consistently describing its invention -- in the Abstract, Background of Invention, Summary of Invention, and Detailed Description sections of the specifications -- as one that solves the ink accumulation problem inherent in the prior art, the ink delivery means cannot be interpreted [*11] apart from the essential cleaning, high-pressure air source.

Plaintiff responds with proof from the prosecution history. Plaintiff's Exhibit 8 at page 58-60 includes a "Species Restriction" wherein the patent examiner found the patent application contained "claims directed to the following patentably distinct species of the claimed invention." In that communication, he directed plaintiff to select one set of claims from a group of three possible inventions described in the original patent application:

(A) A single side ink jet printer with two pressure flows to propel the ink and maintain cleanliness of the nozzles, claims 1-6, 27-32.

(B) A two side ink jet printer, claims 18-30.

(C) A two side ink jet printer with two pressure flows to propel the ink and maintain cleanliness of the nozzles, claims 7-17, 21-26.

(Plaintiff's Exhibit 8 at p. 59). Plaintiff chose Group C, the two side printer with two pressure flows, which became U.S. Patent No. 5,294,946 (the '946 patent). In addition, plaintiff pursued a "continuation application", which eventually became the '957 patent. Plaintiff uses this to suggest that because the examiner found that the claims in Group [*12] C were distinct from those in Group B, the patent which grew out of Group B must not include the distinctive features of those Group C claims, i.e. the two air flows.

The problem with this argument and reliance on these two pages of the prosecution history is that the specifications found in the '957 patent describe much more than a "two side ink jet printer". Rather, the specifications in '957 describe a two side ink jet printer which fixes a problem inherent in the ink delivery means in the prior art; ink accumulation on the nozzles. I heard no evidence explaining the purpose or significance of a continuation application. The parties provided no authorities to me in their otherwise thorough post-trial briefs that direct me to authorities which discuss "species restrictions" and "continuation applications". The principal authority cited by defendant, **Laitram Corp. v. Rexnord, Inc.**, discussed the judicially created guide to claim interpretation known as "claim differentiation" n13 In **Laitram**, plaintiff argued that the interpretation of one claim in a patent dictated the interpretation of another claim; an argument which would have produced a result in conflict [*13] with the interpretation required by § 112(6). In rejecting this analysis, **Laitram** teaches that the statutory "means plus function" claim interpretation required by *35 U.S.C. § 112*(6) is primary. Accordingly, I am bound by the consistent language in the specifications in '957. Because it is undisputed that neither the Vutek Model 3200 nor the 3200i includes a second, high pressure air source, I find that plaintiff has not shown infringement as to that element of Claim 1.

n13 *939 F.2d 1533, 1536 (Fed. Cir. 1991).*

Plaintiff also claims that Vutek's Models 3200 and 3200i infringe the "means for generating control signals" and the "means for controlling the ink delivery means" clauses. Once again, these are "means plus function" clauses which must be interpreted in the context of structure and function.

Figure 6 n14 in '957 shows the following:

[SEE Fig. 6 IN ORIGINAL]

Note that the scanner (51) sends a single signal to the controller (53), which sends a single signal to the modulator (57) which [*14] simultaneously sends a single signal to the each of the four color jets positioned on each side of the substrate (13); the same signal goes to 59A as to 60A, 59B as to 60B, 59C as to 60C, and 59D as to 60D. An alternate embodiment shown in figure 10 shows the front and rear print heads striking the substrate at different times; however, there is no diagram or narrative in the specifications to show two separate sets

of signals coming out of the modulator. n15 And despite plaintiff's insistence, I refuse to equate the word "image" found in the last clause of Claim 1, to "data signal" so as to infer that there are two sets of signals -- one representing the original and one the mirror image -- going to the print heads. There is nothing to support such a reading of the word "image" in the specifications or prosecution history. Rather, the word "image" is used in the specifications consistent with its plain meaning -- a visual representation -- only. Consistent with the other specification diagrams, I must conclude that in figure 10 a single signal for each color ink jet leaves the modulator, and is merely time delayed to accommodate the distance between the front and rear print head. [*15] Aside from one lonely reference in the specification to the possibility that one skilled in the art could print different images on opposite sides of the substrate, n16 in the absence of any diagrams or other references to such an application of the device, and given the clarity of diagrams 6 and 9 showing a single signal to 59A and 60A, another single signal to 59B and 60B, etc., I cannot infer that the device contemplated two entirely different sets of control signals to the opposing print heads. n17

n14 Figure 9 contains an alternate embodiment of the invention, the only difference being that ink valves 59A-D and 60A-D are substituted for air valves 59A-D and 60A-D shown in figure 6.

n15 Figure 10 of the '957 patent:

[SEE Fig. 10 IN ORIGINAL]

n16 Plaintiff's Exhibit No. 1, col. 8, lines 47-55 which reads as follows:

Although print heads 23 and 25 were only described as being synchronously controlled to produce the exact image on both sides of the imaging medium, one of ordinary skill in the art will readily recognize that the print heads could be controlled asynchronously. That is, each print head could be controlled separately to produce either different densities of the same image on opposite sides of the imaging medium or two different images on opposite sides of the imaging medium.

(emphasis added). [*16]

n17 In this regard, I have rejected the "functional block diagram", Plaintiff's Exhibit 74, that Ed Fiorito testified from insofar as it shows two separate signals coming out of the "ink delivery controller means". This block diagram was not part of the specifications or prosecution history and is inconsistent with what I find shown in figures 6 and 9, and with plaintiff's prosecution position with the patent examiner.

Furthermore, the prosecution history supports the above interpretation called for by figures 6 and 9. The Koumura patent n18 covered a double-sided copy machine which scanned an image and then scanned the reverse side of the same image, and sent two electronically different sets of signals to the print heads. In distinguishing its claims from those found in the Koumura patent, plaintiff explained that

Claim 33 includes an ink delivery means controller which receives signals representing a single image and controls an ink delivery means to reproduce the image on one side of a substrate and a mirror image on the opposite side of the substrate.

In contrast, Koumura merely [*17] discloses an ink jet printer that produces an image on both sides of a medium when an original having images on both sides is fed into the apparatus. Koumura includes dual scanners connected separately to dual print heads so that an image from each side of the original may be transferred to the medium. The only way to reproduce the same image on both sides of Koumura is to place an original in the apparatus which already has the same image on both sides. However, the resulting images produced on either side of the medium will not be aligned as an original and its mirror unless the original contains such a configuration. Accordingly, Koumura does not disclose, teach, or suggest an ink delivery means controller which receives signals representing a single image and controls an ink delivery means to reproduce the received image on one side of a substrate and a mirror image on the opposite side of the substrate.

(emphasis added). (Defendant's Exhibit 19, p. 75).

n18 U.S. Patent No. 4,475,128.

Apparently, [*18] the patent examiner continued to have problems differentiating the invention from the Koumura claims. In further response plaintiff repeated:

Applicants respectfully submit that the Koumura apparatus is incapable of producing an image on one side of a recording sheet and a mirror of that same image on the other side of the recording sheet from a single sided original.

***

The claimed invention scans only a single image on a single side of a document and does not scan double sided documents because the control means of the claimed invention regulates the ink delivery means to reproduce the image and its mirror from the single sided original.

(emphasis added). (Defendant's Exhibit No. 19, pp. 89-90). Given the specifications and the prosecution history, I find that the "means for generating control signals" and "means for controlling the ink delivery means" clauses, whether found in the preferred embodiment shown in figure 6, or the alternate embodiments shown in figures 9 and 10, refer to a single set of control signals coming from the modulator to the print heads.

Turning to the alleged infringing devices, defendant admits that Vutek Model 3200 used a single [*19] set of signals, although the signals going to the rear print head were time-delayed because of the manner in which the print heads were offset on the 3200. n19 With the introduction of the Model 3200i in January 1996, defendant created two sets of image files or signals, using Adobe Photoshop software to create a separate, mirror image file of the original image, or by scanning an original and separately scanning its mirror image. The modification was intended to mimic the theory of the Koumura patent, as applied to backlit signs. Having construed the "means for generating control signals" and "means for controlling the ink delivery means" clauses as referring to a single set of control signals to the front and back print heads, I must find the Vutek Model 3200i does not literally infringe '957.

n19 Defendant's Exhibit 29.

Nor does the 3200i infringe under the doctrine of equivalents. Without addressing whether this claim is properly before the Court, for all of the reasons set forth above, I find that plaintiff [*20] has not met its burden to show that the accused device "performs substantially the same overall function or work, in substantially the same way, to produce substantially the same overall result as the claimed invention" (emphasis added). n20 It does not use a second high pressure air source to clean the print heads and enhance the image quality, nor does it use a single set of electronic signals to control the front and rear print heads.

n20 ***Graver Tank & Mfg. Co. v. Linde Air Products Co.***, *339 U.S. 605, 608, 94 L. Ed. 1097, 70 S. Ct. 854 (1950);* ***Dolly, Inc. v. Spalding & Evenflo Companies, Inc.***, *16 F.3d 394 at 397 (Fed. Cir. 1994).*

Having found that plaintiff has failed to show that either of defendant's devices infringe '957, it is unnecessary to consider the invalidity and unenforceability arguments advanced by defendant.

II. The '522 Patent - Invalidity and Damages

I have previously found that plaintiff's Model DH1600 infringed the '522 patent, specifically reserving ruling [*21] on the defenses based on invalidity for trial. After considering the evidence and arguments of counsel, I find that plaintiff has failed to show by clear and convincing evidence that the '522 patent is invalid as anticipated by or obvious in light of the prior art. *35 USC § 102*(b) and § 103.

Plaintiff argues that the Jayne patent (U.S. Patent No. 4,839,666) contains all of the elements of the claims found in the '522 patent and that in light of Jayne, defendant's invention would have been obvious to one of ordinary skill in the art at the time it was made (1988). As noted above, plaintiff has the burden to prove invalidity by clear and convincing evidence. n21 For a patent claim to be anticipated under *35 U.S.C. § 102*(b), all the elements in the claim must be disclosed in a single prior art reference or device, n22 arranged as in that claim. n23 The test for obviousness is whether the pulse-width modulation invention found in '522 as a whole was obvious to someone skilled in the art in 1988. n24 In order to assess the obviousness challenge to '522, I must assess the scope and content of the prior art, the differences between the prior art and the claims at issue, the level [*22] of ordinary skill in the art in 1988, and objective evidence of nonobviousness. n25 Objective evidence of nonobviousness includes commercial success of the invention, failure of others, long-felt need and unexpected results. n26

n21 ***SSIH Equipment S.A. v. U.S. Intern. Trade Comm'n***, *718 F.2d 365, 375 (Fed. Cir. 1983);* ***Trans-World Mfg. Corp. v. Al Nyman & Sons, Inc.***, *750 F.2d 1552, 1559 (Fed. Cir. 1984);* ***Ralston Purina Co. v. Far-Mar-Co., Inc.***, *772 F.2d 1570, 1574 (Fed. Cir. 1985);* ***Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.***, *730 F.2d 1452, 1459 (Fed. Cir. 1984);* ***Jones v. Hardy***, *727 F.2d 1524, 1528 (Fed. Cir. 1984);* ***Jamesbury Corp. v. Litton Industrial Products, Inc.***, *756 F.2d 1556, 1559 (Fed. Cir. 1985),* **cert. denied,** *488 U.S. 828, 102 L. Ed. 2d 57, 109 S. Ct. 80 (1988).*

n22 ***Motorola, Inc. v. Interdigital Technology Corp.***, *121 F.3d 1461, 1997 WL*

429908, *11 (Fed. Cir. 1997); ***SSIH Equipment, S.A. v. U.S. International Trade Commission,*** *718 F.2d 365, 377 (Fed. Cir. 1983).*

n23 ***Carella v. Starlight Archery and Pro Line Co.,*** *804 F.2d 135, 138 (Fed. Cir. 1986)* (quoting ***Panduit Corp. v. Dennison Manufacturing Co.,*** *774 F.2d 1082, 1101 (Fed. Cir. 1985)).* [*23]

n24 ***Hybritech, Inc. v. Monoclonal Antibodies, Inc.,*** *802 F.2d 1367, 1383 n. 6 (Fed. Cir. 1986),* **cert. denied,** *480 U.S. 947, 94 L. Ed. 2d 792, 107 S. Ct. 1606 (1987)* (obviousness question is whether the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made, not at a later time when presumably the prior art and level of ordinary skill in the art are more advanced).

n25 ***Specialty Composites v. Cabot Corp.,*** *845 F.2d 981, 989 (Fed. Cir. 1988);* ***Environmental Designs, Ltd. v. Union Oil Co. of California,*** *713 F.2d 693, 695 (Fed. Cir. 1983),* **cert. denied,** *464 U.S. 1043, 79 L. Ed. 2d 173, 104 S. Ct. 709 (1984).*

n26 ***Hybritech, Inc. v. Monoclonal Antibodies, Inc.,*** *802 F.2d at 1380.*

The Jayne patent which issued in 1988, disclosed a device with four modulators, one that controlled the airflow to the ink jet, two that modulated the ink supply to the jet, and one that changed the size of the ink orifice. While Jayne taught that the combination of the modulators [*24] could be changed, it did not teach that one could omit all but the modulator which controlled the duration of the airflow. In fact, in one mode of operation, it suggests elimination of the modulator controlling the flow of gas. n27 The other modes of operation teach modulation of only the ink orifice, or the gas flow rate (amplitude of the air pressure), n28 and counsel that both the gas and ink modulators must be used to ensure reliability. n29

n27 Plaintiff's Exhibit 28, col. 4, line 61-68.

n28 Plaintiff's Exhibit 28, col. 5, lines 1-21 and col. 5, lines 20-36.

n29 Plaintiff's Exhibit 28, col. 3, lines 39-44.

In contrast, the invention disclosed in '522 involves only modulation of the duration of the constant pressure airflow and will not function if other aspects of the ink delivery means, such as the ink supply, the ink orifice or rate of air pressure, are modulated as Jayne suggests. Further, the objective evidence shows that neither Jayne nor anyone else was successful in building a printer [*25] incorporating the invention shown in the Jayne patent, that the Vutek printers incorporating the '522 invention were highly successful commercially, and that even plaintiff, acknowledging the value of the '522 invention, acquired a license to sell the Vutek printers in 1988-1990, and purchased a total of eleven Vutek printers. Accordingly, Jayne supports neither the anticipation nor obviousness defenses put forth by plaintiff.

Damages

The parties stipulated as part of the Pretrial Order that a reasonable royalty of $ 10,000 for each of plaintiff's fourteen infringing DH1600 printers was appropriate. The basic damage award is therefore $ 140,000. I also find and so hold that defendant is entitled to prejudgment interest on this award at the three-month Treasury Bill rate. n30

n30 The award of prejudgment interest is authorized by ***General Motors Corp. v. Devex Corp.,*** *461 U.S. 648, 657, 76 L. Ed. 2d 211, 103 S. Ct. 2058 (1983)* (prejudgment interest should generally be awarded absent some justification for withholding such an award). The three-month Treasury Bill rate for the interest calculation advocated by defendant's witness, Richard Troxel, was unchallenged by defendant, and I find it to be appropriate. I obtained the three-month rates for the months since September 30, 1996 from the Federal Reserve Board's World Wide Web site and have applied those rates to the Troxel figures found in Defendant's Exhibit No. 122.

[*26]

Defendant further argues that because the Final Pretrial Order lists as a contested fact whether plaintiff ever actually made a change in its printers to omit the pulse-width modulation, and because plaintiff alone was in a position to prove its non-infringement (with evidence more credible than the testimony of plaintiff's principal, James Gandy), I should infer that plaintiff failed to make the critical change in its printers and find that an additional 24 printers infringed '522. I refuse to shift the burden of proof in this manner. In the absence of proof to the contrary, I find that the testimony was

credible on this point and find that infringement as to the fourteen printers only has been shown.

In addition to the basic damage award, defendant asks that I find that plaintiff's infringement was willful and that I accordingly award enhanced damages. Defendant shoulders the burden of proof to show willfulness by clear and convincing evidence. n31 I am instructed to look at the totality of circumstances, n32 and focus on whether or not plaintiff intentionally copied the invention, as opposed to having accidentally adopted it. n33 A finding of willful infringement is warranted [*27] where an infringer deliberately copies the patented product after recognizing the product's commercial success and improvement over the art and failing to develop its own non-infringing version. n34

n31 ***Shatterproof Glass Corp. v. Libbey-Owens Ford Co.***, *758 F.2d 613, 628 (Fed. Cir. 1985).*

n32 ***Shiley, Inc. v. Bentley Laboratories, Inc.***, *794 F.2d 1561, 1568 (Fed. Cir. 1986),* **cert. denied,** *479 U.S. 1087, 94 L. Ed. 2d 148, 107 S. Ct. 1291 (1987).*

n33 ***Stryker Corp. v. Intermedics Orthopedics, Inc.***, *96 F.3d 1409, 1414 (Fed. Cir. 1996).*

n34 ***Spindelfabrik Suessen-Schurr Stahlecker & Grill GmbH v. Schubert & Salzer Maschinenfabrik Aktiengesellschaft***, *829 F.2d 1075, 1085 (Fed. Cir. 1987),* **cert. denied,** *484 U.S. 1063, 108 S. Ct. 1022, 98 L. Ed. 2d 987 (1988).*

I have previously found that plaintiff's DH1600 incorporated pulse width modulation so as to infringe the '522 patent. At trial I heard evidence from which I conclude and specifically find that [*28] the DH1600 also incorporated important circuitry from the Vutek 800 which controlled and operated the pulse width modulation.

As noted above, defendant applied for a patent on the pulse width modulation invention in April 1989, the year Vutek Model 800 was first sold. The '522 patent issued in April 1990. In 1988 plaintiff entered into a licensing agreement to sell Vutek printers. In 1989 or 1990, Vutek principals met with James Gandy to discuss adding a second print head to the Model 800 to print on the front and back of a substrate. Later, in August 1990, defendant terminated the licensing agreement after plaintiff failed to pay for five printers shipped to plaintiff in 1989 and 1990. Plaintiff continued to purchase Vutek 800s after the termination.

Plaintiff began production of the DH1600 in 1992 and sold 14 such printers which used the pulse width modulation. Gary Ferran testified that in 1992 when he was hired by plaintiff as Senior Project Manager to work on its ink jet printers, Signtech was about to ship a DH1600 printer, which was very unreliable and in a primitive stage of development. However, he found no schematics outlining the logic or technical documentation for the [*29] DH1600, no circuit boards for the DH1600, no software listings for the firmware used on the DH1600 controller boards, no materials lists, no inventor source lists of where parts were purchased, nor chips -- nothing which reflected the development of that printer. Instead, he found schematics with defendant's name on them, controller boards that he believed were Vutek's (since he did not believe Signtech had the ability to produce the boards and the logic on the boards matched the Vutek schematics), and defendant's "golden chip" or PROM on which was implanted Vutek's "firmware" which directed the controller board, and in turn controlled the operation of the print head, stepping motor for the vinyl, and air valves for the inkjets. Ferran testified that while he was employed at Signtech from 1992-94, he was directed to copy the Vutek 800 controller board schematics, Vutek firmware, and later Vutek's software program, all of which would improve the functioning and reliability of the Signtech product.

Plaintiff argues that I should discredit Ferran's testimony because of his obvious bias against his former employer. Plaintiff also argues that defendant failed to establish a nexus between [*30] the documents Ferran produced for the first time at trial and Signtech, and suggests that it was entirely reasonable for Signtech to have had possession of defendant's schematics and even the "golden chip" because of the prior licensing relationship between the parties and its continuing obligation to repair Vutek machines and sometimes replace parts such as the "golden chip".

While plaintiff's argument is plausible, it does not explain why Ferran's schematics were identical, even to the arbitrary reference numbers for the parts or computer chips, to those of the Vutek 800 ... with the addition in the Ferran schematics of circuitry to control a second print head. Nor does it explain the absence of any documentary or other evidence that would support the independent development of the DH1600. While Ferran could have easily been shown to have been a disgruntled ex-employee and therefore lacking in credibility, plaintiff alone was in a position to produce rebuttal evidence to discredit Ferran with objective evidence, rather than innuendo and insinuation. I was never shown any of plaintiff's schematics or firmware by plaintiff so as to

have distinguished what Ferran produced from [*31] what plaintiff actually used on the DH1600. Apparently, none was produced during discovery either, despite timely requests for same. The objective documentary evidence fully supports Ferran's testimony that he was instructed to copy the controller board schematics, that the schematics he brought to trial were the schematics used by plaintiff in its DH1600 printers, and that plaintiff copied the "golden chip" and used those copies in its DH1600.

The objective evidence also supports Ferran's testimony that he was instructed to copy Vutek software program used to generate the control signals to run the pulse width modulation. While in Italy in January 1994, tasked with "acquiring" Vutek's software program used to generate control signals, apparently a last act in the copying venture necessary to improve the reliability of the DH 1600, James Gandy sent Ferran a fax advising Ferran that Signtech had acquired the Vutek software it needed. Ferran produced this document at trial. n35 This "smoking gun", along with the other compelling evidence noted above, and the evidence that the machines even looked similar (at a time when web printing and horizontal rails for print head were otherwise [*32] unusual), leads to no reasonable conclusion other than that plaintiff intentionally copied defendant's machine, including the pulse width modulation protected by '522. The totality of the evidence dictates the conclusion that the infringement of the '522 patent was no accident, but deliberate.

n35 Defendant's Exhibit 120.

In further support of its claim of willful infringement, defendant argues that plaintiff failed to obtain competent legal advice before incorporating the pulse width modulation invention in its DH1600 printer. Plaintiff responds that it had a reasonable, good faith belief that its conduct would not constitute infringement after it sought the advice of counsel in 1991 and was advised that the '522 patent was invalid in light of Jayne. n36 Based on this advise, plaintiff obtained a license to use the Jayne patent in 1993. Plaintiff supports this version of the facts with the testimony of James Gandy, principal of Signtech, Don Comuzzi, plaintiff's patent attorney, and Christopher Makay, who was [*33] then a patent examiner, now an attorney, working with Comuzzi. Through these witnesses, plaintiff attempted to offer into evidence testimony concerning a now-lost opinion letter from Comuzzi to Gandy, the existence of which was not disclosed until just before trial despite timely pretrial discovery requests by defendant. Despite the obvious significance of the letter at the time it was written and later, neither Gandy nor Comuzzi were able to locate during discovery or at trial, a copy of the letter, notes used to prepare the letter, or billing records to substantiate the research for and drafting of the letter. In addition, Gandy testified that the opinion was so important that it was discussed at a meeting of plaintiff's Board of Directors, although no minutes of that meeting were introduced at trial.

n36 ***Underwater Devices Inc. v. Morrison-Knudsen Co., Inc.,*** *717 F.2d 1380, 1389-90 (Fed. Cir. 1983)* (no willful infringement if infringer acted with counsel's advise).

The only possible independent support [*34] for plaintiff's position is the undisputed evidence offered through James Gandy that plaintiff did obtain a license to use the Jayne patent. Plaintiff listed Jayne as a trial witness to testify on this point, but did not call him. However, this evidence does not necessarily lead to the conclusion that plaintiff reasonably believed, based on the opinion of counsel, that '522 was invalid because of Jayne. In light of the other evidence heard, this evidence doesn't invalidate the inference that there was no opinion or that, if there was an opinion letter, it was contrary to the plaintiff's desire to initiate or continue its use of defendant's invention. n37 Given these facts, defendant's objection to the oral testimony of Gandy, Comuzzi and Makay concerning the existence of the opinion is sustained and that testimony is stricken from the record. I refuse to find that plaintiff ever obtained an opinion from competent counsel concerning its potential infringement of the '522 patent. In addition, any opinion counseling that '522 was invalid based on anticipation in light of Jayne, was not reasonable for all the reasons recited above, and any oral opinion given by a patent agent not yet licensed [*35] to practice law was incompetent. It is undisputed that plaintiff knew of the '522 patent; it was intimately familiar with the invention from its servicing of the Vutek 800 machines; it failed to obtain an opinion from counsel and did not have a reasonable, good faith belief in the invalidity of '522. The evidence viewed in its totality is clear and convincing and dictates a finding of willful copying. Further, I find that these facts warrant an award a trebling of the basic damage award of $ 140,000, and because I find that the case is "exceptional", an attorneys fees award is appropriate. n38

n37 ***Fromson v. Western Litho Plate & Supply Co.,*** *853 F.2d 1568, 1572-73 (Fed. Cir. 1988).*

n38 *35 U.S.C. § 285.*

Finally, defendant seeks a permanent injunction against plaintiff for any further infringement, inducement of infringement or contributory infringement of the '522 patent, which I find warranted and so order. n39

n39 *35 U.S.C. § 283.*

[*36]

Conclusion

For all the above reasons, I conclude that plaintiff has failed to show defendant infringed the '957 patent. I further conclude that defendant is entitled to a basic damage award of $ 140,000 for infringement by plaintiff of the '522 patent, prejudgment interest in the amount of $ 28,818, plus enhanced damages of $ 420,000 for plaintiff's willful infringement of the '522 patent, a permanent injunction against plaintiff for any further infringement of the '522 patent, and attorney's fees in an amount to be determined upon submission of appropriate affidavits. n40

n40 **See** Local Rule CV-7(j).

SIGNED on September 30, 1997.

NANCY STEIN NOWAK

United States Magistrate Judge

LEXSEE 2001 us app lexis 14275

DUREL CORPORATION, Plaintiff-Cross Appellant, v. OSRAM SYLVANIA INC., Defendant-Appellant.

00-1261, -1391

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2001 U.S. App. LEXIS 14275

June 27, 2001, Decided

PRIOR HISTORY:
[*1] Appealed from: United States District Court for the District of Arizona. Senior Judge Edward Rafeedie.

DISPOSITION:
REVERSED-IN-PART and VACATED-IN-PART.

CASE SUMMARY

PROCEDURAL POSTURE: Defendant appealed from the judgment of the United States District Court for the District of Arizona holding that it infringed defendant's patents, from partial summary judgment dismissing its counterclaim for declaratory judgment of invalidity for failure to meet the enablement requirement of *35 U.S.C.S. § 112,* and denial of its motion for a new trial on damages. Defendant cross-appealed from the finding of no willful infringement.

OVERVIEW: The appellate court held the district court erred in its construction of the term "oxide coating." The specification defined it as a material made up primarily of metal cations and oxygen, but which could contain minor amounts of other elements and compounds originating in the precursor materials or phosphor particles. It required that the coating primarily comprise metal oxide compounds, binary compounds containing only metal cations and oxygen. The lower court failed to give meaning to the established term metal oxide and to the specification's consistent use of that term. Given that there was no infringement, remand was not necessary as to the doctrine of equivalents. Defendant's coatings contained an additional element, hydrogen, and therefore did not meet the claim limitation. The erroneous application of enablement law was compounded by the erroneous claim construction. Without any record as to whether the disclosure enables the preparation of oxide coatings within the scope of the claims, the appellate court was unable to conclude whether the claims were fully enabled. Remand to consider the validity of a patent that was not infringed was a poor use of judicial resources.

OUTCOME: The court of appeals reversed the court's judgment of infringement. The remaining issues relating to infringement were moot. The appellate court vacated the district court's grant of partial summary judgment that the patents were not invalid.

CORE CONCEPTS

Patent Law : Infringement : Claim Interpretation
Patent Law : Infringement : Acts of Infringement
A determination of patent infringement requires a two-step analysis. First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device or process. Literal infringement requires that every limitation of the patent claim be found in the accused device.

Patent Law : Jurisdiction & Review : Standards of Review
Patent claim construction is an issue of law, that an appellate court reviews de novo. Whether a claim encompasses an accused device, either literally or under the doctrine of equivalents, is an issue of fact that, following a bench trial, the court of appeals reviews for clear error. Enablement is a question of law, based on underlying factual inquiries, that the appellate court reviews de novo.

Patent Law : Infringement : Claim Interpretation

A court is free to consult dictionary definitions to interpret patent claim terms, so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents.

Civil Procedure : Appeals : Reviewability : Preservation for Review
An appellee is not expected to defend a judgment in its favor on the basis of a theory of liability that was never presented to the fact-finder.

Patent Law : Infringement : Doctrine of Equivalents
If a theory of equivalence would vitiate a claim limitation, then there can be no infringement under the doctrine of equivalents as a matter of law.

Patent Law : Specification & Claims : Enablement Requirement
The dispositive question of enablement does not turn on whether the accused product is enabled. Rather, to be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

Patent Law : Specification & Claims : Enablement Requirement
Enablement is a question of law based on underlying factual determinations.

Patent Law : Specification & Claims : Enablement Requirement
The enablement requirement is met if the description enables any mode of making and using the invention.

COUNSEL:
Laurence H. Pretty, Christie, Parker & Hale, LLP, of Pasadena, California, argued for plaintiff-cross appellant. Of counsel was John David Carpenter.

Robert G. Krupka, Kirkland & Ellis, of Los Angeles, California, argued for defendant-appellant. With him on the brief were John M. Desmarais, and Robert A. Appleby, Kirkland & Ellis, of New York, New York; and Christopher Landau, Kirkland & Ellis, of Washington, DC. Of counsel was Jay I. Alexander, Kirkland & Ellis, of Washington, DC.

JUDGES:
Before LOURIE, Circuit Judge, PLAGER, Senior Circuit Judge, and GAJARSA, Circuit Judge.

OPINIONBY:
LOURIE

OPINION:

LOURIE, Circuit Judge.

Osram Sylvania Inc. ("Sylvania") appeals from the judgment of the United States District Court for the District of Arizona holding that Sylvania infringed Durel Corporation's U.S. Patents *5,418,062*, *5,439,705*, and *5,156,885*. *Durel Corp. v. Osram Sylvania Inc., 1998 U.S. Dist. LEXIS 22592, 52 USPQ2d 1418, 1435 (D. Ariz. 1998)*. Sylvania also appeals from the district court's grant of partial summary [*2] judgment dismissing Sylvania's counterclaim for declaratory judgment of invalidity for failure to meet the enablement requirement of *35 U.S.C. § 112*. Id. Finally, Sylvania appeals from the district court's denial of its motion for a new trial on damages. Durel Corp. v. Osram Sylvania Inc., No. 95-1750 (D. Ariz. Apr. 13, 2000). Durel cross-appeals from the district court's denial of its motion for judgment as a matter of law that Sylvania willfully infringed the *'885* patent. Durel Corp. v. Osram Sylvania Inc., No. 95-1750 (D. Ariz. Apr. 21, 2000). Durel also cross-appeals from the denial of its motion to award damages for the period between the close of discovery and entry of the injunction. Durel Corp. v. Osram Sylvania Inc., No. 95-1750 (D. Ariz. May 4, 2000). Because the district court erred in its construction of the term "oxide coating" and Sylvania's coatings do not infringe Durel's patents as a matter of law, we reverse.

BACKGROUND

Durel is the exclusive licensee n1 of the *'062*, *'705*, and *'885* patents, which relate to encapsulated electroluminescent ("EL") phosphor particles used in applications such as illuminating watch faces and instrument [*3] panels in motor vehicles. Encapsulating phosphor particles within the claimed oxide coatings increases the particles' resistance to deterioration attributable to atmospheric humidity. *Durel, 52 USPQ2d at 1420*. All of the independent claims of the patents recite that the phosphor is encapsulated by an "oxide coating." Claim 1 of the *'062* patent claims a product (in relevant part) as follows:

1. Encapsulated electroluminescent phosphor particles, each comprising a particle of zinc sulfide-based electroluminescent phosphor which is essentially completely encapsulated within a substantially transparent, continuous metal oxide coating ....

'062 patent, col. 14, ll. 24-28 (emphasis added). The specification of each patent defines "oxide coating" as follows:

As used herein, "oxide coating" means a material made up primarily of metal cations and oxygen, but which may contain minor amounts of other elements and

compounds originating in the precursor materials or phosphor particles, which can be generated in coating form on phosphor particles under the conditions described herein. Advantageous results have been obtained with coatings of titania [*4] (TiO[2]) and titania/silica TiO[2]/(SiO[2]). It is believed that useful results may also be obtained with other oxides formed from precursors in low temperature reactions such as silica (SiO[2]), alumina (Al[2]O[3]), tin oxide (SnO[2]), zirconia (ZrO[2]), etc., and similarly formed compound oxides such as mullite (3Al[2]O[3]. 2SiO[2]).

'062 patent, col. 5, ll. 36-49; *'885* patent, col. 5, ll. 33-45; *'705* patent, col. 5, ll. 36-49 (emphasis added).

> n1 Sylvania does not dispute that Durel has standing to bring this patent infringement suit without joining the owner of the patents, Minnesota Mining and Manufacturing Co. ("3M"). We nevertheless have addressed the question whether Durel possesses all substantial rights under the patent such that it has standing to sue without joining 3M because that question is jurisdictional. See *Mentor H/S, Inc. v. Med. Device Alliance, Inc., 240 F.3d 1016, 1018, 57 USPQ2d 1819, 1821 (Fed. Cir. 2001)*. We have reviewed the license agreement between 3M and Durel and conclude that Durel received all substantial rights under the patent within the meaning of *Vaupel Textilmaschinen v. Meccanica Euro Italia, 944 F.2d 870, 875-76, 20 USPQ2d 1045, 1049 (Fed. Cir. 1991)*, and may therefore sue for infringement without joining 3M.

[*5]

The patents each disclose the same twenty-eight examples, three of which coat phosphor with TiO[2]/SiO[2]; the remaining twenty-five examples coat phosphor with TiO[2]. *'062* patent, col. 11, ll. 55 to col. 14, ll. 22. The oxide coating can be formed by the hydrolysis reaction of precursor molecules such as titanium tetrachloride (TiCl[4]) and water, which react in the vapor phase to produce TiO[2] and hydrochloric acid. Id. at col. 6, ll. 41-52. Moreover, a high ratio of titanium tetrachloride molecules to water molecules is maintained "to promote the formation of more anhydrous titania films which are believed to provide optimum protection against humidity-accelerated decay." Id. at col. 7, ll. 20-22. If encapsulation is performed at low temperatures, the coatings may be insufficiently moisture impermeable, "a result it is believed of having a more open or more hydrated structure." Id. at col. 8, ll. 12-13.

Sylvania manufactures two types of phosphors relevant to this appeal: EL-type phosphors coated by a fluidized-bed reaction of water vapor and trimethyl aluminum; and newly encapsulated ("NE")-type phosphors coated by a water-free pyrolysis reaction of [*6] trimethyl aluminum, oxygen, and ozone. It is undisputed on appeal that the coatings on both the EL- and NE-type phosphors are a mixture of aluminum oxide hydroxide, AlO(OH), and aluminum trihydroxide, Al(OH)[3]. *Durel, 52 USPQ2d at 1429.*

Durel sued Sylvania for infringement of its *'062*, *'705*, and *'885* patents by the EL-type phosphors. Id. at 1427. The district court construed the term "oxide coating" as being primarily composed of metal cations and oxygen, but also possibly containing other elements or compounds found in the original precursor ingredients or phosphor particles. Id. at 1428. The court then concluded that "a synthetic chemist would interpret the [patents] by using atomic mass to determine whether a coating is primarily metal cations and oxygen atoms with minor amounts of other elements and compounds found in the precursors." Id. at 1428. The court calculated that AlO(OH) is composed of approximately 43.3% aluminum, 53.3% oxygen, and 3.4% hydrogen, and that Al(OH)[3] n2 is composed of 49.1% aluminum, 45.3% oxygen, and 5.6% hydrogen. n3 Id. at 1429. Finally, the court concluded that AlO(OH), containing 96.6% metal cations and oxygen [*7] and 3.4% other elements, and Al[2](OH)[3], containing 94.4% metal cations and oxygen and 5.6% other elements, fell squarely within its construction of the term "oxide coating." Id. Sylvania's coatings contained at least 94.4% aluminum and oxygen, satisfying the "primarily" requirement of the court's definition of "oxide coating." Id. The court concluded that the amount of hydrogen, at most 5.6%, was minor in light of the amount of metal cations and oxygen in the coating. Id. Moreover, because the court found that hydrogen originated from water, which is defined in the specification as a precursor compound, it fell within the definition of the minor (non-metal or oxygen) ingredients of the coating. Id. The court therefore concluded that Sylvania's coating satisfied the oxide coating claim requirement and granted partial summary judgment to Durel. Id.

> n2 The court used an incorrect formula for aluminum trihydroxide, viz., Al[2](OH)[3], in its calculation. That error, however, was immaterial because the percentage of hydrogen present is small in both Al(OH)[3] and Al[2](OH)[3]. [*8]
>
> n3 The court stated that its calculations were based on the atomic masses of the most commonly found isotopes of aluminum, oxygen,

and hydrogen. *Durel, 52 USPQ2d at 1429.* We question whether it did so, because it apparently used the atomic number, representing the number of protons, rather than atomic mass, which is an average value based on an element's isotopic composition and includes both protons and neutrons. Steven S. Zumdahl, Chemistry 75 (2d ed. 1989). Aluminum's atomic number is 13 and its atomic mass is 26.98; oxygen's atomic number is 8 and its atomic mass is 16.00; and hydrogen's atomic number is 1 and its atomic mass is 1.008. Id. Therefore, using atomic masses, AlO(OH) contains 1.7% hydrogen and Al(OH)[3] contains 3.9% hydrogen. That error was also not material.

Finally, the court dismissed Sylvania's counterclaim for declaratory judgment of invalidity for lack of enablement under *35 U.S.C. 112,* P 1, concluding that Sylvania had not proven by clear and convincing evidence that Durel's patents were nonenabling. Id. at 1435. The court [*9] stated that "the only question at issue in this proceeding is whether Durel's patents fail to enable without undue experimentation a trimethyl aluminum precursor ("TMA") and alumina coating as used by [Sylvania]." Id. at 1432. The court then granted partial summary judgment to Durel, holding that the patents were enabled because it found that undue experimentation was not required to make an alumina-coated EL-type phosphor from the known TMA precursor. Id. at 1435. Because "the only precursor and coating at issue in this case is TMA and alumina," the court did not follow through with its observation that "it is apparent that some of the precursors or coating material suggested by Durel would require undue experimentation." Id.

Sylvania then began manufacturing NE-type phosphors, which are produced by pyrolysis, and moved for summary judgment of noninfringement with respect to those phosphors, arguing that claim 1 of the *'062* patent is limited to phosphors produced by hydrolysis. The court declined to construe the claim as being limited to hydrolysis and denied Sylvania's motion. Durel Corp. v. Osram Sylvania Inc., No. 95-1750 (D. Ariz. Feb. 12, 1999) (order). Sylvania [*10] stipulated to infringement based on the court's claim construction and a trial was held on damages and willfulness. The jury returned a damages verdict of almost $ 50 million but declined to find that the infringement was willful.

DISCUSSION

A determination of infringement requires a two-step analysis. *Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1476, 45 USPQ2d 1498, 1500 (Fed. Cir. 1998).* "First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device or process." Id. "Literal infringement requires that every limitation of the patent claim be found in the accused device." *Gen. Mills, Inc. v. Hunt-Wesson, Inc., 103 F.3d 978, 981, 41 USPQ2d 1440, 1445 (Fed. Cir. 1997).* Claim construction is an issue of law, *Markman v. Westview Instruments, Inc., 52 F.3d 967, 970-71, 34 USPQ2d 1321, 1322 (Fed. Cir. 1995)* (en banc), aff'd, *517 U.S. 370, 134 L. Ed. 2d 577, 116 S. Ct. 1384 (1996),* that we review de novo, *Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456, 46 USPQ2d 1169, 1172 (Fed. Cir. 1998)* [*11] (en banc). Whether a claim encompasses an accused device, either literally or under the doctrine of equivalents, is an issue of fact that, following a bench trial, we review for clear error. *WMS Gaming, Inc. v. Int'l Game Tech., 184 F.3d 1339, 1346, 51 USPQ2d 1385, 1389 (Fed. Cir. 1999).* Enablement is a question of law, based on underlying factual inquiries, that we review *de novo. Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1369, 52 USPQ2d 1129, 1134 (Fed. Cir. 1999).*

A. Claim Construction

Sylvania argues that the district court erred in its construction of the term "oxide coating," urging that the definition in the specification requires that the coating be primarily composed of metal oxides, which are binary compounds, and that the "other elements and compounds" it may contain are only impurities of the coating. Thus, according to Sylvania, the primary metal oxide molecule of the coating may not itself contain other elements such as hydrogen that would make that molecule something that is not classifiable as a metal oxide. Sylvania also argues that the court erred in its conclusion that claim 1 of the *'062* patent is not limited [*12] to phosphors produced by hydrolysis.

Durel responds that the court correctly adopted the special definition of the term "oxide coating" set forth in the specification, which includes metal cations, oxygen, and minor amounts of another element such as hydrogen. Durel urges that a definition that excludes the presence of hydrogen would exclude a preferred embodiment in the specification because all of the examples of metal oxides in the specification inherently include some hydroxide in their hydrated form. Durel also urges that claim 1 of the *'062* patent is not limited to phosphors produced by hydrolysis.

We agree with Sylvania that the district court erred in its construction of the term "oxide coating." We rely primarily on the definition in the specification, which defines "oxide coating" as "a material made up primarily of metal cations and oxygen, but which may contain

minor amounts of other elements and compounds originating in the precursor materials or phosphor particles." *'062* patent, col. 5, ll. 37-40 (emphasis added). We conclude that this language requires that the "oxide" coating must primarily comprise metal oxide compounds, viz., binary compounds containing [*13] only metal cations and oxygen. This definition is supported by the examples that immediately follow in the specification, all of which are binary compounds containing only metal cations and oxygen: TiO[2], TiO[2]/SiO[2], SiO[2], Al[2]O[3], SnO[2], ZrO[2], and 3Al[2]O[3] . 2SiO[2]. According to the specification, the coating may indeed contain "minor amounts of other elements and compounds originating in the precursor materials or phosphor particles," such as water or hydroxides, but it may not be composed primarily of compounds that are not binary metal oxides.

This interpretation is also supported by dictionary definitions of "metal oxide," which we are free to consult to interpret claim terms, "so long as the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents." *Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1584 n.3, 39 USPQ2d 1573, 1578 n.3 (Fed. Cir. 1996).* Compounds containing additional elements other than metal and oxygen are not generally classified as metal "oxides." See, e.g., McGraw-Hill Dictionary of Scientific and Technical Terms 1425 (5th ed. 1994) (defining [*14] "oxide" as a "binary chemical compound in which oxygen is combined with a metal"); Hawley's Condensed Chemical Dictionary 861 (12th ed. 1993) (defining "oxide" as "[a] mineral in which metallic atoms are bonded to oxygen atoms"). The district court's principal error in its claim construction was in using calculations of atomic mass percent to interpret the "primarily" language. In doing so, it failed to give meaning to the established term "metal oxide" and to the specification's consistent use of that term.

We are not persuaded by Durel's argument that this definition excludes a preferred embodiment of metal hydroxides that are (allegedly) inherently present in the disclosed metal oxides. We find no disclosure of metal hydroxides in the specification. Durel cites a reference showing that the term alumina trihydrate (Al[2]O[3]. 3H[2]O) may be used interchangeably with aluminum trihydroxide Al(OH)[3]. n4 Even accepting that this may be true in some circumstances, it is not relevant here. The specification teaches that oxide hydration should be minimized, see, e.g., *'062* patent, col. 7, ll. 15-22 (stating that the ratio of tetrachloride molecules to water molecules [*15] should be high to promote the formation of optimal anhydrous titania films) (emphasis added), thereby indicating that compounds that are primarily hydrates and hydroxides are not intended. Moreover, if the inventor had intended to equate metal oxides with metal hydroxides, he could have so stated and avoided exclusively exemplifying metal oxides as binary compounds. Therefore, according to the specification's explicit definition of "oxide coating" and its description of such coatings, the claimed oxide coating must primarily comprise binary metal oxides containing only metal cations and oxygen. Other elements and compounds originating in precursor materials, such as hydrated metal oxides or metal hydroxides, if present at all, may only be present in minor amounts as impurities. Accordingly, we conclude that the district court erred in construing the term "oxide coating" as not requiring a primary component that is a binary metal oxide.

n4 Alumina as a Ceramic Material 3-4 (Walter H. Gitzen, ed., 1970).

[*16]

B. Infringement

We also agree with Sylvania that the district court clearly erred in finding infringement. In Sylvania's opening brief, Sylvania requested that we remand this case for a new determination of infringement if we disagree with the court's claim construction. At oral argument, however, Sylvania changed its request, stating that a judgment of noninfringement as a matter of law would be appropriate because Durel acknowledged in its response brief that the coatings on the accused EL- and NE-type phosphors are both mixtures of AlO(OH) and Al(OH)[3]. We agree and conclude that there is no genuine issue of material fact concerning infringement under a proper construction of the term "oxide coating." As we have held, the claimed "oxide coating" must primarily comprise a binary compound or compounds containing only metal cations and oxygen. It is undisputed that the accused phosphor coatings primarily comprise compounds containing hydrogen (H) as hydroxide (OH), in addition to metal cations (Al) and oxygen (O), rather than binary metal oxides. The hydroxide is part of the primary metal compound itself; it is not present as a mere impurity of the coating material. Thus, [*17] Sylvania's accused hydroxide coatings do not meet the definition of the claim limitation "oxide coating." We therefore reverse the district court's grant of partial summary judgment of infringement.

The district court did not reach the question whether Sylvania's AlO(OH) and Al(OH)[3] phosphor coatings infringe the "oxide coating" limitation under the doctrine of equivalents. Although Durel did not raise that issue on appeal, it did not thereby surrender its ability to argue

that issue altogether. An appellee is not expected to defend a judgment in its favor on the basis of a theory of liability that was never presented to the fact-finder. *Exxon Chem. Patents, Inc. v. Lubrizol Corp., 137 F.3d 1475, 45 USPQ2d 1865, 1868 (Fed. Cir. 1998).* When the district judge construed the claim language in Durel's favor, the doctrine of equivalents issue in the case became moot. See id. The doctrine of equivalents only became a critical issue after our disagreement with the court's claim construction and reversal of its finding of literal infringement.

We decline to remand the case for the district court to hear arguments on infringement under the doctrine of equivalents, [*18] however, because we conclude that no reasonable fact-finder could find such infringement. As we have construed the claims, the "oxide coating" must primarily comprise binary compounds containing only metal cations and oxygen. Sylvania's AlO(OH) and Al(OH)[3] coatings contain an additional element, hydrogen, and therefore do not meet the claim limitation that only metal cations and oxygen be present in the primary component of the oxide coating. A finding of equivalence would vitiate the limitation "oxide coating," which we have concluded is defined to primarily consist of a binary compound. See *Tronzo v. Biomet, Inc., 156 F.3d 1154, 1160, 47 USPQ2d 1829, 1834 (Fed. Cir. 1998)* ("If a theory of equivalence would vitiate a claim limitation, however, then there can be no infringement under the doctrine of equivalents as a matter of law."). We therefore conclude that Sylvania's coatings do not infringe Durel's patents under the doctrine of equivalents. We decline to reach the question whether claim 1 of the *'062* patent is limited to an oxide coating produced by hydrolysis, as that question is mooted by our conclusion of noninfringement of the oxide coating limitation. [*19]

C. Enablement

Sylvania asserts that the court erred in dismissing its enablement defense because the court treated lack of enablement as a "personal defense." At a minimum, Sylvania requests that we vacate the district court's judgment and permit Sylvania to demonstrate at trial that undue experimentation is necessary to practice the claimed invention. Specifically, Sylvania asserts that the inventor, Kenton D. Budd, was only able to make an alumina coating from a TMA precursor after referring to Sylvania's own disclosure in U.S. Patent *5,080,928*, and that he could not make it from a dimethyl aluminum chloride precursor. Sylvania also asserts that the invention is not enabled because Budd was unable to obtain a moisture-resistant or hermetic coating with a titanium isopropoxide precursor, which is one of the precursors suggested in the specification. Sylvania finally argues that Budd had difficulty preparing silicon dioxide coatings from the silicon ethoxide precursor disclosed in the specification, and that Budd could not successfully make a zinc oxide coating.

Durel responds that it was not improper for the district court to consider the accused products in its enablement [*20] analysis, and that the court's focus on the accused products must be viewed in light of the court's additional conclusion "that [Sylvania] has not provided clear and convincing evidence that the Durel patents fail to enable one skilled in the art as required by section 112, paragraph 1, for every suggested precursor and oxide coating found in the Durel patents." *Durel, 52 USPQ2d at 1432.* Moreover, Durel argues that an alumina coating from TMA was enabled in a Rothschild patent, and that Budd did not learn of the *'928* patent until after he had successfully produced an alumina coating from TMA. Durel also argues that dimethyl aluminum chloride was not a suggested precursor and that, in any event, the alumina coating is enabled by the TMA precursor. Durel also asserts that the patent enables a titanium dioxide coating made from the titanium tetrachloride precursor, and that enablement by one precursor is sufficient to satisfy the statutory requirement. Durel argues that Budd's experimentation to make the silicon dioxide coating was not undue. Finally, Durel argues that Budd's inability to make the zinc oxide coating does not render the claim invalid under our decision [*21] in *Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 414 (Fed. Cir. 1984).*

Although we have concluded that Sylvania does not infringe Durel's patents, the validity of these patents has been placed in issue by Sylvania's declaratory judgment counterclaim. Accordingly, we will address its enablement arguments in order to correct the district court's erroneous analysis. See *Cardinal Chem. Co. v. Morton Int'l, Inc., 508 U.S. 83, 98, 26 USPQ2d 1721, 1728, 124 L. Ed. 2d 1, 113 S. Ct. 1967 (1993)* (holding that the Federal Circuit abused its discretion in not ruling on a declaratory judgment counterclaim concerning validity when noninfringement had been found); see, e.g., *N. Am. Vaccine, Inc. v. Am. Cyanamid Co., 7 F 3d 1571, 1579, 28 USPQ2d 1333, 1339 (Fed. Cir. 1993)* (deciding both noninfringement and validity issues).

The district court dismissed Sylvania's counterclaim seeking a declaratory judgment of invalidity for lack of enablement, stating that "the only question at issue in this proceeding is whether Durel's patents fail to enable without undue experimentation [use of] a trimethyl aluminum [*22] precursor ("TMA") [to make an] alumina coating as used by [Sylvania]." *Durel, 52 USPQ2d at 1432.* We agree with Sylvania that the court thus made an error of law. The dispositive question of enablement does not turn on whether the accused product

is enabled. Rather, "to be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech, Inc. v. NovoNordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997)* (emphasis added). If Sylvania had shown that a significant percentage of oxide coatings within the scope of the claims were not enabled, that might have been sufficient to prove invalidity. See *Atlas Powder, 750 F.2d at 1576-77, 224 USPQ at 414* ("If the number of inoperative combinations becomes significant, and in effect, forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid.").

The district court's erroneous application of enablement law was then further compounded by what we have now concluded was its erroneous [*23] claim construction. Having found that Sylvania's AlO(OH) and Al(OH)[3] coatings were within the scope of the claims, and enabled, the court ended its enablement inquiry. Those coatings are in fact irrelevant to enablement because they are outside the scope of the claims as we have construed them, whereas a fuller set of fact-findings within the scope of the claims would have been needed to decide the enablement issue. The court therefore erred in determining that the claims were not invalid based only on its conclusion that coatings outside the scope of the claims were enabled.

The district court did not express any ultimate opinion as to enablement of other oxide coatings within the scope of the claims, although, significantly, it stated without further explanation that "it is apparent that some of the precursors or coating material suggested by Durel would require undue experimentation." *Durel, 52 USPQ2d at 1435.*

Enablement is a question of law based on underlying factual determinations. *Enzo, 188 F.3d at 1369, 52 USPQ2d at 1134.* Without any specific factual determinations in the record below regarding whether the disclosure enables the preparation [*24] of oxide coatings within the scope of the claims, we are unable to conclude as a matter of law whether the claims are fully enabled. We put to rest, however, Sylvania's argument that the patent is not enabled because the inventors failed to prepare coatings from each of the precursors suggested in the specification. If the disclosure enables a person of ordinary skill in the art to make a particular metal oxide coating from at least one of the suggested precursors, the enablement requirement for that oxide coating is satisfied. See *Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998)* (stating that the enablement requirement is met if the description enables any mode of making and using the invention). The court's statement that use of some metal precursors would require undue experimentation, even if true, would therefore not be fatal to the validity of the claim if the patent specification enabled the preparation of the particular metal oxide coating asserted to be non-enabled from another precursor of that metal. For example, if the patent specification enabled a person of ordinary skill in the art to make the claimed titanium [*25] dioxide coating from a titanium tetrachloride precursor, it would be irrelevant for purposes of validity if the patent specification did not enable its preparation from a titanium isopropoxide precursor.

Although Sylvania's arguments with respect to precursors are off the mark, Sylvania could still have succeeded in its enablement defense if it had proved that the disclosure does not enable someone of ordinary skill in the art to make oxide coatings within the full scope of the claims. We cannot decide this question without specific factual findings. If our noninfringement conclusion were not an adequate basis for our decision, we would vacate the district court's grant of partial summary judgment that Durel's claims are enabled and the patent is hence not invalid and remand the case for a determination whether the disclosure adequately enables the scope of the claims. However, under the circumstances, a remand is not necessary. Remand to consider the validity of a patent that we have held not to be infringed would be a poor use of judicial resources. We simply vacate the district court's grant of partial summary judgment that the patents are not invalid.

In view of our reversal [*26] of the district court's grant of partial summary judgment of infringement, we need not consider Sylvania's appeal from the denial of its motion for a new trial or Durel's cross-appeals on willfulness and damages.

The issues in this case have not been easy ones to decide and the district court carefully and conscientiously waded through the issues. While we have reversed the district court, we do so with the recognition that the issues are not ones of clear-cut certainty about which reasonable differences cannot exist.

CONCLUSION

Because the district court erred in its interpretation of the term "oxide coating" and the accused coatings do not meet that claim limitation as a matter of law, we reverse the court's judgment of infringement. The remaining issues relating to infringement are moot. Accordingly, we

REVERSE-IN-PART and VACATE-IN-PART.

LEXSEE 2001 us app lexis 8888

BERNARD DALSIN MANUFACTURING COMPANY, Plaintiff-Appellant, v. RMR PRODUCTS, INC., Defendant-Appellee.

00-1308

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2001 U.S. App. LEXIS 8888

May 7, 2001, Decided

NOTICE:
[*1] RULES OF THE FEDERAL CIRCUIT COURT OF APPEALS MAY LIMIT CITATION TO UNPUBLISHED OPINIONS. PLEASE REFER TO THE RULES OF THE UNITED STATES COURT OF APPEALS FOR THIS CIRCUIT.

DISPOSITION:
Reversed and Remanded.

CASE SUMMARY

PROCEDURAL POSTURE: Plaintiff appealed the judgment from the decision of the United States District Court for the District of Minnesota, which granted the motion of defendant for summary judgment of non-infringement of a patent.

OVERVIEW: Plaintiff was the assignee of the patent at issue, which related to a chimney damper attachable to the top of a chimney flue. Plaintiff contended that the district court improperly construed a claim limitation. The court agreed with the appellant that the district court erred, and found defendant's arguments in support of the district court's conclusions to be unpersuasive. There was no requirement in the claim that an additional intervening structure be absent, and also, the use of attaching the damper plate to the flue was not necessarily substantially different from the structure used in the patent. The court concluded that a reasonable jury could have found infringement under a proper construction of the claim limitation.

OUTCOME: The court reversed and remanded the decision finding that the district court erred in its infringement analysis, and that under a proper claim construction there remained a genuine issue of material fact concerning infringement.

CORE CONCEPTS

Civil Procedure : Appeals : Appellate Jurisdiction
An appellate court has jurisdiction over an appeal pursuant to *28 U.S.C.S. § 1295*(a)(1).

Civil Procedure : Summary Judgment : Summary Judgment Standard
An appellate court reviews a district court's grant of a motion for summary judgment without deference.

Patent Law : Jurisdiction & Review : Standards of Review
Patent Law : Infringement : Acts of Infringement
A patent infringement analysis requires two steps. First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device or process. Claim construction is a matter of law that is reviewed de novo. Determination of infringement, whether literal or under the doctrine of equivalents, is a question of fact.

Patent Law : Infringement : Claim Interpretation
35 U.S.C.S. § 112, para. 6, states that a means-plus-function claim shall be construed to cover the corresponding structure, materials, or acts described in the specification and equivalents thereof. The determination of the corresponding structure of a means-plus-function claim is a determination of the meaning of the means term, and is a matter of claim construction.

Patent Law : Specification & Claims : Claim Language

The question of equivalents infringement under *35 U.S.C.S. § 112,* para. 6, is generally a question of literal infringement though the standards applied are similar to doctrine of equivalents infringement.

Patent Law : Infringement : Acts of Infringement
It is well-established that the presence of additional structure, such as an intervening structure, in an accused device will not exclude a finding of infringement.

Patent Law : Infringement : Acts of Infringement
Whether an accused device or method infringes a claim with a *35 U.S.C.S. § 112,* para. 6, limitation, i.e., whether it performs the identical function with the same structure, materials, or acts described in the specification or an equivalent thereof, is a question of fact.

JUDGES:
Before LOURIE, RADER, and DYK, Circuit Judges.

OPINIONBY:
DYK

OPINION:

DYK, Circuit Judge.

Bernard Dalsin Manufacturing Company ("Dalsin") appeals from the decision of the United States District Court for the District of Minnesota granting the motion of RMR Products, Inc. ("RMR") for summary judgment of non-infringement of U.S. Patent No. *4,554,863* (the " *'863* patent"). Bernard Dalsin Mfg. Co. v. RMR Prods., Inc., No. 98-CV-1149 (D. Minn. Sept. 14, 1999) ("Dalsin"). We find that the district court erred in its infringement analysis, and that under a proper claim construction there remains a genuine issue of material fact concerning infringement. Therefore we reverse the grant of summary judgment of non-infringement, and remand to the district court for further proceedings.

BACKGROUND

Dalsin is the assignee of the *'863* patent, which relates to a chimney damper attachable to the top of a chimney flue. The patent addresses the shortcomings of traditional dampers installed [*2] near the base of the flue which often do not adequately seal the air passageway, thereby allowing cold air to enter the dwelling even when the damper is in the closed position. *'863* patent, col. 1, ll. 20-23. The patent also addresses numerous shortcomings of dampers designed to be installed at the top of the flue, for example, that they are often heavy, expensive, and particularly subject to mechanical failure. Id. at ll. 24-39. The chimney damper described in the *'863* patent is attachable to the top of the chimney flue and includes a frame that is mountable to the open periphery of the chimney flue and has a superior portion extending above the flue opening. Id. at ll. 42-48. A spring extends between a flue cover that seals the flue opening and the superior portion of the frame, and a control mechanism is used to open and close the flue cover. Id. at ll. 51-55.

Figures 1 and 8 of the *'863* patent illustrate a preferred embodiment as follows:

[SEE FIGURES 1 AND 8 IN ORIGINAL]

As illustrated in the embodiment shown in Figures 1 and 8, the chimney damper 20 is mounted to the top portion of a flue 16 of a chimney 15. Id. at col. 2, ll. 39-41. The chimney damper includes [*3] a frame 22 with a superior portion 22.1 extending above the flue opening. Id. at ll. 46-50. The chimney damper also includes a flue cover in the form of a damper plate 21. Id. at ll. 53-58. An extension spring 24 extends from the superior portion 22.1 of the frame 22 to suspend the damper plate 21 above the flue opening when the chimney damper is in the open position shown in Figures 1 and 8. The damper plate 21 is connected to a vertically movable stem 33, and the stem is operatively linked by a cable 35 to a control device (not shown) remotely mounted within the fireplace opening. Id., col. 3, ll. 10-14. By operating the control device, the damper plate 21 may be pulled downward from the open position shown in Figures 1 and 8 to a closed position so that the damper plate engages the top surface of the flue, thereby sealing the inside of the chimney flue from the exit or entrance of air or particles. Id. at ll. 14-21.

In the embodiment shown in Figures 1 and 8, the stem 33 is guided in the vertical direction by a fixed stem guide 34 supported in the center of the flue opening by rods 30 and 31 and tubes 32. *'863* patent, col. 4, ll. 51-58. The rods and tubes are secured [*4] to the flue 16 by means of mounting brackets 23. In the embodiment shown in Figures 1 and 8, mounting screws 39 secure the mounting bracket 23 against the wall of the flue 16. The frame 22 is also mounted to the mounting brackets 23.

The *'863* patent contains seven claims. Independent claim 1, the only claim at issue in this appeal, reads as follows:

1. A chimney damper attachable to a chimney flue having an upwardly facing, generally planar peripheral surface defining an upwardly open flue opening, comprising:

(a) a frame mountable to the open periphery of a chimney flue and having a superior portion oriented to extend above said flue opening;

(b) flue cover means comprising a thin, generally rectangular metal plate having a generally planar

peripheral portion to seal against the upwardly facing surface of a flue opening;

(c) mounting means for mounting the flue cover means to the chimney flue;

(d) spring means extending between the flue cover means and the superior portion of the frame for spring biasing the flue cover means upwardly away from the flue opening, the flue cover means serving to protect the spring means from heated gases emanating from the flue opening; [*5] and

(e) control means for urging the flue cover means downwardly, in opposition to the spring means, into sealing contact with a flue opening, the control means including lock means for maintaining the flue cover in its sealing position.

Id. at col. 6, l. 52 to col. 7, l. 7 (emphasis added).

Dalsin sued RMR, asserting that RMR had infringed claim 1 of the *'863* patent by making, using, and selling an "Icebreaker" chimney damper and a "Universal" chimney damper. On February 24, 1999, RMR filed motions for summary judgment on the issues of non-infringement, invalidity, and damages. On September 14, 1999, the district court granted RMR's motion for summary judgment of non-infringement, but denied the motions for summary judgment related to invalidity and damages as moot in light of its grant of the non-infringement motion. Dalsin, slip op. at 2.

In its order, the district court agreed that "the Icebreaker and Universal are similar to the chimney damper in the patent and obviously serve the same general purpose. Indeed, RMR's products contain some features that are virtually identical to the elements of the patented product." Id., slip op. at 17. In finding non-infringement, [*6] the district court construed claim 1, particularly focusing on the "mounting means for mounting the flue cover means to the chimney flue." The district court agreed with the parties that the "mounting means" limitation was a means-plus-function limitation under *35 U.S.C. § 112*, paragraph 6. Id., slip op. at 13. The district court then found, contrary to Dalsin's assertion, that the "mounting means" comprises more than just the structure necessary to mount the mounting brackets to the chimney flue, i.e., the "screws, rivets, bolts, glue, or silicone" described in the specification. Id., slip op. at 15. Instead, the district court included the entire structure that it thought was necessary to mount the flue cover to the chimney flue. The district court noted: "The mounting means therefore comprises some set of components equivalent to the screws, springs, brackets, rods, and stem guide apparatus described in the specification which together serve the function of mounting the flue cover means to the inside of the chimney flue." Id. (emphasis added).

The district court then performed the second step of the infringement analysis and held that [*7] the Icebreaker and Universal dampers do not literally infringe because they do not have the mounting means set forth in the patent. The district court stated that: "Specifically, the Icebreaker's flange, the center locator, and the s.s. cable, are not means for mounting the alleged flue cover means (the damper plate) to the inside of the flue. Similarly, the Universal's cross-bar, upper portion of the s.s. cable, and chimney cap anchor do not mount the damper plate to the flue." Id., slip op. at 16. The court also held that the Icebreaker and Universal dampers do not infringe under the "doctrine of equivalents," meaning apparently that the accused devices did not have structures equivalent to the "mounting means" structure found in the specification because, inter alia, "the screws and silicon that attach these cap-damper products to the flue are substantially different and serve an entirely different function than the mounting means in the patent." Id. The district court therefore granted RMR's motion for summary judgment of non-infringement. On March 14, 2000, the district court entered final judgment on the infringement claim as authorized by Fed. R. Civ. P. 54(b) and [*8] stayed further proceedings on the remaining claims pending final disposition on appeal. Dalsin then appealed to this court.

DISCUSSION

I. Jurisdiction and Standard of Review

We have jurisdiction over this appeal pursuant to *28 U.S.C. § 1295*(a)(1) (1994). We review a district court's grant of a motion for summary judgment without deference. *Ethicon Endo-Surgery, Inc. v. United States Surgical Corp., 149 F.3d 1309, 1315, 47 USPQ2d 1272, 1275 (Fed. Cir. 1998).*

A patent infringement analysis requires two steps. *Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1476, 45 USPQ2d 1498, 1500 (Fed. Cir. 1998).* "First, the claim must be properly construed to determine its scope and meaning. Second, the claim as properly construed must be compared to the accused device or process." Id. (quoting *Carroll Touch, Inc. v. Electro Mech. Sys., Inc., 15 F.3d 1573, 1576, 27 USPQ2d 1836, 1839 (Fed. Cir. 1993)).* Claim construction is a matter of law that is reviewed de novo. *Cybor Corp. v. FAS Techs., Inc., 138 F.3d 1448, 1456, 46 USPQ2d 1169, 1174 (Fed. Cir. 1998)* (en banc). Determination [*9] of infringement, whether literal or under the doctrine of equivalents, is a question of fact. *Bai v. L & L Wings, Inc., 160 F.3d 1350, 1353, 48 USPQ2d 1674, 1676 (Fed. Cir. 1998).*

II. Claim Construction and Infringement

The primary issues in this appeal concern the "mounting means for mounting the flue cover means to the chimney flue" limitation of claim 1. The parties do not dispute that the "mounting means" limitation is a means-plus-function limitation invoking *35 U.S.C. § 112*, paragraph 6. We agree.

Section 112, paragraph 6 states that a means-plus-function claim "shall be construed to cover the corresponding structure, materials, or acts described in the specification and equivalents thereof." The determination of the corresponding structure of a means-plus-function claim is a determination of the meaning of the "means" term, and is a matter of claim construction. *Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus., Inc., 145 F.3d 1303, 1308, 46 USPQ2d 1752, 1756 (Fed. Cir. 1998).* Dalsin urges that the district court improperly construed the "mounting means" limitation. n1

n1 As we have stated repeatedly, the question of equivalents infringement under § 112, paragraph six, is generally a question of literal infringement though the standards applied are similar to doctrine of equivalents infringement. See *Kemco Sales, Inc. v. Control Papers Co., 208 F.3d 1352, 1364, 54 USPQ2d 1308, 1315-16 (Fed. Cir. 2000)* (noting that "section 112, paragraph 6 equivalents must perform the identical function of the disclosed structure while equivalents under the doctrine of equivalents need only perform a substantially similar function" and that "because the 'way' and 'result' prongs are the same under both the section 112, paragraph 6 and doctrine of equivalents tests, a structure failing the section 112, paragraph 6 test under either or both prongs must fail the doctrine of equivalents test for the same reason(s)") (internal citations omitted); *IMS Tech., Inc. v. Haas Automation, Inc., 206 F.3d 1422, 1435-36, 54 USPQ2d 1129, 1138-39 (Fed. Cir. 2000); Chiuminatta, 145 F.3d at 1310-11, 46 USPQ2d at 1757-58.*

[*10]

The first question is: what is the corresponding structure described in the specification for the mounting means? The district court correctly defined the "flue cover means" to be the damper plate. Although in general the district court appears to have correctly identified the structure corresponding to the "mounting means," in order to avoid any possible confusion we set forth below the proper construction.

In determining the structure corresponding to the mounting means we must first determine what structure described in the specification performs the mounting means function. The specification describes a variety of structure that could arguably perform a mounting means function, including the frame which is attached to the mounting brackets, and the spring. The specification, while not a model of clarity, focuses on the stem guide, stem, screws, and mounting brackets as the structure which mounts the flue cover means, i.e., the damper plate, to the chimney flue. See, e.g., *'863* patent, col. 4, ll. 49-65. Dalsin argues that the mounting means of the *'863* patent cannot include the stem and stem guide. This argument is not persuasive.

We reject also Dalsin's assertion [*11] that the mounting means is directed toward mounting the frame to the flue, instead of the flue cover to the flue. Claim 1 expressly recites "mounting means for mounting the flue cover means to the chimney flue." Dalsin urges that "the only structure necessary to mount the flue cover means to the chimney flue is that structure which mounts the frame to the chimney flue." This argument is unpersuasive because the stem, stem guide, mounting brackets, and mechanism for attaching the mounting brackets to the chimney flue, i.e., mounting screws, all of which are described in the specification, comprise the structure necessary for performing the function of mounting the flue cover, i.e., the damper plate, to the chimney flue. The frame and the structure necessary to attach the frame itself to the mounting brackets and flue are not part of this "mounting means."

We turn then to the comparison of the claim to the accused devices. The district court found that there was "no dispute of material fact as to whether the Icebreaker or Universal literally infringe element (c) [the mounting means limitation]," meaning apparently that they do not have identical structure to that shown [*12] in the specification. Dalsin, slip op. at 15. This remains undisputed. However, the district court also found that the Icebreaker and Universal do not have equivalent structures because "Dalsin has offered no evidence from which a finder of fact could reasonably conclude that the Icebreaker and Universal have components that serve substantially the same function as the mounting means in the patent, perform the function in substantially the same way as the mounting means, or will achieve substantially the same results as the mounting means." Id., slip op. at 16.

We agree with the appellant that the district court erred, and we find RMR's arguments in support of the district court's conclusions to be unpersuasive.

RMR makes several arguments in support of its claim of non-infringement. First RMR says that its devices do not contain "mounting means" at all because these devices do not perform the function of mounting the damper plate to the chimney flue. This is so because there is intervening structure positioned between the damper plate and the top of the chimney flue in the accused devices, i.e., the interior ledge around the bottom opening of each of the Icebreaker [*13] and Universal dampers, against which the damper plate rests when it is in the closed position. In both the Icebreaker and Universal devices, the damper plate does not directly contact the top of the chimney flue when it is in its closed position. RMR asserts that because the damper plate is not directly mounted to the chimney flue in either of the accused products, a finding of infringement is precluded. However, it is well-established that the presence of additional structure, such as the intervening structure, in the accused device will not exclude a finding of infringement, *SunTiger, Inc. v. Scientific Research Funding Group, 189 F.3d 1327, 1336, 51 USPQ2d 1811, 1816-17 (Fed. Cir. 1999); A.B. Dick Co. v. Burroughs Corp., 713 F.2d 700, 703, 218 USPQ 965, 967-68 (Fed. Cir. 1983),* cert. denied, *464 U.S. 1042, 79 L. Ed. 2d 171, 104 S. Ct. 707 (1984),* and there is no requirement in the claim here that such additional structure be absent.

Second, RMR argues that the mechanism for attaching the damper plate to the flue in the accused product is substantially different from the structure used in the *'863* patent. Specifically RMR urges [*14] that its use of glue in the Universal and Icebreaker dampeners is substantially different from the patented chimney damper which the specification shows attached by a plurality of mounting screws. This argument similarly must fail. The claims cover equivalents to the mounting screws as well as the mounting screws themselves. A genuine issue of material fact exists as to whether a reasonable juror could conclude that the use of glue is equivalent to the use of screws.

Third, RMR argues that the accused damper devices do not contain separate mounting brackets and therefore do not have the mounting means structure disclosed in the specification. The relevant question however is whether the accused devices effectively incorporate the mounting brackets disclosed in the specification or equivalents thereof. Again, the issue of equivalent structure is a question of fact, resolution of which is inappropriate here on summary judgment because there are disputed issues of fact.

Fourth, RMR argues that the cable, crossbar, and holes in the crossbar for the cable in the Icebreaker are not equivalent structure to the stem and stem guide described in the patent specification. The Icebreaker device [*15] includes a metal guide crossbar with two guide holes which serves as a guide for a cable loop attached to the damper plate. The two guide holes are spaced apart on the guide bar in order to prevent the damper plate from twisting when the cable is pulled downward to move the damper plate toward the closed position. The district court concluded: "While the components ... may serve some of the same general purposes as the mounting means in element (c), such as reducing unwanted shifting of the damper plate (flue cover), these features cannot be considered equivalent. These components do not stabilize the damper plate by mounting it to the flue." Dalsin, slip op. at 16.

Dalsin did not present affidavit evidence to show the correspondence between the Icebreaker structure and the stem and stem guide structure disclosed in the specification and equivalents thereof. However, photographs of the Icebreaker device and the affidavit of RMR's president raise a genuine issue of material fact as to whether the Icebreaker device includes structure equivalent to the stem and stem guide. The photographs and RMR affidavit show the cable, guide crossbar, and guide holes of the Icebreaker device [*16] assisting in resisting rotation of the damper plate while the damper plate is being pulled downward by the cable loops. The guide crossbar and guide holes also resist horizontal movement by the damper plate when it is being pulled downward.

As RMR contends, the cable, guide crossbar, and guide holes of the Icebreaker device probably do not perform the function of mounting the damper plate to the chimney flue when the damper plate is in the open position. However, the mounting means is concerned only with mounting the damper plate in the closed position. The spring means support the damper plate in the open position. The issue as to whether equivalent structure to the stem and stem guide are present in the Icebreaker device is a close one, and we do not decide this issue as a matter of law. *IMS Tech., Inc. v. Haas Automation, Inc., 206 F.3d 1422, 1430, 54 USPQ2d 1129, 1134 (Fed. Cir. 2000)* ("Whether an accused device or method infringes a claim with a § 112, P6 limitation, i.e., whether it performs the identical function with the same structure, materials, or acts described in the specification or an equivalent thereof, is a question of fact."); *Odetics, Inc. v. Storage Tech. Corp., 185 F.3d 1259, 1268-69, 51 USPQ2d 1225, 1230-31 (Fed. Cir. 1999).* [*17]

Likewise, there is a genuine issue of material fact as to whether the Universal chimney damper includes equivalent structure to the stem and stem guide. The Universal chimney damper, which was also shown in photographs and described in the RMR president's affidavit, also uses a cable, a guide crossbar, and cable

holes that allegedly restricts rotation and horizontal movement of the damper plate.

We of course do not address the correctness of the claim construction of other claim limitations other than the "mounting means" limitation. These issues were not raised in this appeal, and we also express no opinion as to whether an issue of material fact has been raised concerning infringement under these other limitations. Nor do we address the district court's conclusions concerning the period of available damages. See Dalsin, slip op. at 17 n.10.

Thus, because we conclude that a reasonable jury could have found infringement under a proper construction of the mounting means limitation of claim 1, we reverse the district court's grant of summary judgment of non-infringement and remand to the district court for further proceedings consistent with this opinion.

COSTS

No costs.

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LEXSEE 1996 us dist lexis 22529

DAP PRODUCTS, INC., Plaintiff, vs. SASHCO, INC., Defendant.

Case No. C-3-92-407

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF OHIO, WESTERN DIVISION

1996 U.S. Dist. LEXIS 22529

July 17, 1996, Decided

July 17, 1996, Filed

DISPOSITION:

[*1] Defendant's Motion for Partial Summary Judgment (Doc. # 61) OVERRULED as to its Counterclaims and Count Three of Plaintiff's Complaint and OVERRULED as moot, without prejudice to renewal, in regard to Counts One and Two of Plaintiff's Complaint. Plaintiff's Motion for a Hearing (Doc. # 62) on said motion (Doc. # 61) SUSTAINED, nunc pro tunc March 1, 1996. Plaintiff's Motion for Partial Summary Judgment (Doc. # 64) OVERRULED in part and SUSTAINED in part. Plaintiff's Motion to Compel Defendant's Expert Witness to answer certain deposition questions (Doc. # 66); Plaintiff's alternative Motion to Strike Mr. Bross as an Expert Witness (Doc. # 66); Defendant's Motion for a Protective Order (Doc. # 72); Plaintiff's Motion to Exclude Evidence of Defendant's New Damage Theories (Doc. # 74); and Defendant's Motion to Compel the Plaintiff to Answer Interrogatories (Doc. # 78) OVERRULED as moot. Declaratory judgment of non-infringement of Defendant's '458 patent and Defendant's '014 patent entered, pursuant to Rule 54(b), in favor of the Plaintiff and against the Defendant. Judgment on the Defendant's Counterclaims entered, pursuant to Rule 54(b), in favor of the Plaintiff and against the Defendant. [*2]

COUNSEL:

For DAP PRODUCTS INC, plaintiff: David Alan Shough, Killworth, Gottman, Hagan & Schaeff, Paul Gerard Hallinan, Faruki, Gilliam & Ireland, Dayton, OH.

For SASHCO, INC, defendant: Jerome Charles Randolph, Keating, Muething & Klekamp, Cincinnati, OH.

For SASHCO, INC, defendant: Timothy J Martin, Lakewood, CO.

For SASHCO, INC, defendant: Susan R Fox, Englewood, CO.

For SASHCO, INC, counter-claimant: Jerome Charles Randolph, Keating, Muething & Klekamp, Cincinnati, OH.

For SASHCO, INC, counter-claimant: Timothy J Martin, Lakewood, CO.

For SASHCO, INC, counter-claimant: Susan R Fox, Englewood, CO.

For DAP PRODUCTS INC, counter-defendant: David Alan Shough, Killworth, Gottman, Hagan & Schaeff, Paul Gerard Hallinan, Faruki, Gilliam & Ireland, Dayton, OH.

JUDGES:

WALTER HERBERT RICE, UNITED STATES DISTRICT JUDGE.

OPINIONBY:

WALTER HERBERT RICE

OPINION:

DECISION AND ENTRY OVERRULING DEFENDANT'S MOTION FOR PARTIAL SUMMARY JUDGMENT (DOC. # 61) AS TO ITS COUNTERCLAIMS AND COUNT THREE OF PLAINTIFF'S COMPLAINT; DECISION AND ENTRY

OVERRULING AS MOOT DEFENDANT'S MOTION FOR PARTIAL SUMMARY JUDGMENT REGARDING PLAINTIFF'S FIRST AND SECOND COUNTS, WITHOUT PREJUDICE TO RENEWAL IF [*3] CLAIMS ARE DEEMED VIABLE; DECISION AND ENTRY SUSTAINING, NUNC PRO TUNC MARCH 1, 1996, PLAINTIFF'S MOTION FOR A HEARING ON THE AFORESAID MOTION (DOC. # 62); DECISION AND ENTRY SUSTAINING IN PART AND OVERRULING IN PART PLAINTIFF'S MOTION FOR PARTIAL SUMMARY JUDGMENT (DOC. # 64); DECISION AND ENTRY OVERRULING AS MOOT PLAINTIFF'S MOTION TO COMPEL DEFENDANT'S EXPERT WITNESS TO ANSWER CERTAIN DEPOSITION QUESTIONS (DOC. # 66); DECISION AND ENTRY OVERRULING AS MOOT PLAINTIFF'S MOTION TO STRIKE DEFENDANT'S EXPERT WITNESS (DOC. # 66); DECISION AND ENTRY OVERRULING AS MOOT DEFENDANT'S MOTION FOR A PROTECTIVE ORDER (DOC. # 72); DECISION AND ENTRY OVERRULING AS MOOT PLAINTIFF'S MOTION TO EXCLUDE EVIDENCE OF DEFENDANT'S NEW DAMAGE THEORIES (DOC. # 74); DECISION AND ENTRY OVERRULING AS MOOT DEFENDANT'S MOTION TO COMPEL PLAINTIFF TO ANSWER INTERROGATORIES (DOC. # 78); PARTIES DIRECTED TO INFORM THIS COURT, WITHIN THREE (3) DAYS OF THE DATE OF THIS DECISION, OF THE STATUS OF COUNTS ONE AND TWO OF PLAINTIFF'S COMPLAINT; ENTRY OF DECLARATORY JUDGMENT OF NON-INFRINGEMENT TO BE ENTERED FOR PLAINTIFF AS TO BOTH PATENTS AT ISSUE IN THIS LITIGATION, PURSUANT TO RULE 54(b); ENTRY OF JUDGMENT ON DEFENDANT'S [*4] COUNTERCLAIMS TO BE ENTERED FOR PLAINTIFF AND AGAINST DEFENDANT, PURSUANT TO RULE 54(b); CLERK OF COURTS TO WAIT SEVEN (7) DAYS FROM DATE OF THIS DECISION BEFORE FILING ENTRIES OF JUDGMENT

This is a patent case involving the manufacture and sale of two transparent caulking products by Plaintiff Dap Products, Inc. ("Dap"), which are alleged to infringe patents held by Defendant Sashco, Inc. ("Sashco"). In its Complaint (Doc. # 1), Plaintiff Dap sues the Defendant upon the following claims for relief: false advertising, in violation of the Lanham Act, *15 U.S.C. § 1125*(a) (Count One); deceptive trade practices and unfair competition, in violation of O.R.C. § 4165.01 et seq. and Ohio common law (Count Two); and a request for declaratory judgment of patent invalidity, unenforceability and non-infringement (Count Three). In its Counterclaims (Doc. # 29), Defendant Sashco sues the Plaintiff for infringement of its '458 patent in violation of *35 U.S.C. § 271* (Counterclaim One), and infringement of its '014 patent in violation of *35 U.S.C. § 271* (Counterclaim Two).

This Court has federal question jurisdiction over [*5] Count One pursuant to *28 U.S.C. § 1331*. This Court has original jurisdiction over Count Three pursuant to *28 U.S.C. § 1338*, which grants to federal courts exclusive jurisdiction over civil actions relating to patents. n1 Furthermore, this Court has original jurisdiction over Count Two pursuant to *28 U.S.C. § 1338*(b), which provides that "the district courts shall have original jurisdiction of any civil action asserting a claim of unfair competition when joined with a substantial and related claim under the copyright, patent, plant variety protection or trade-mark laws."

n1 Specifically, this section provides: "The district courts shall have original jurisdiction of any civil action arising under any Act of Congress relating to patents, plant variety protection, copyrights and trade-marks. Such jurisdiction shall be exclusive of the courts of the states in patent, plant variety protection and copyright cases." *28 U.S.C. § 1338*(a).

[*6]

Currently pending before this Court are the parties' motions for partial summary judgment and numerous discovery motions. This Court will address the summary judgment motions in detail before turning to the remaining motions.

Defendant has filed, pursuant to Rule 56 of the Federal Rules of Civil Procedure, a Motion for Partial Summary Judgment (Doc. # 61) with respect to both of its Counterclaims, Plaintiff's request for a declaratory judgment of non-infringement (Count Three), and Counts One and Two of Plaintiff's Complaint as they relate to acts occurring on or before September 20, 1991. Plaintiff has filed a Motion for Partial Summary Judgment (Doc. # 64) with respect to its request for declaratory judgments of non-infringement, invalidity and unenforceability (Count Three), and both of the Defendant's Counterclaims.

In regard to the Defendant's Motion for Partial Summary Judgment as to Counts One and Two of the Plaintiff's Complaint, n2 this Court notes that the Defendant has indicated that the Plaintiff has withdrawn these claims for relief (Doc. # 69, p.2). Nothing in the record before this Court shows that these claims have been formally withdrawn by the Plaintiff. However, [*7] this Court does note that these Counts were not subsequently briefed by the parties, and, further, that

although the Plaintiff had sufficient opportunity to refute the Defendant's assertion regarding the withdrawal of these claims--in both its later pleadings and in the oral argument which was held before this Court on March 1, 1996--Plaintiff did not do so. Therefore, this Court OVERRULES as moot Defendant's Motion for Partial Summary Judgment (Doc. # 61) as to Counts One and Two of Plaintiff's Complaint, without prejudice to renewal, and ORDERS the parties to inform this Court, within three (3) days of the date of this decision, as to the status and viability of these claims for relief.

n2 Remarks by Defendant's counsel over an open telephone line, before the commencement of a telephone conference with this Court, indicated that counsel was "mystified" by this Court's oral ruling, made prior to the issuance of this opinion, on Counts One and Two. Defendant's counsel apparently forgot that he had, on behalf of the Defendant, requested partial summary judgment on these Counts as to any claim for damages before September 20, 1991. See Doc. # 61, p.1 ("Sashco also requests summary judgment that DAP Products' claims against Sashco for alleged false advertising and unfair competition are limited in time to acts after September 20, 1991."). The Court hopes that counsel is no longer mystified as to its ruling on this issue, and, more to the point, that he has learned the lesson that radio personalities have known for generations, to wit: never talk in an audible voice if there is a possibility of an open microphone nearby.

[*8]

This Court now turns to the remaining claims and counterclaims at issue. For the reasons that follow, this Court concludes that, while there exists a genuine issue of material fact as to the validity and enforceability of the Defendant's patents, the Plaintiff's products which are involved in this case do not infringe those patents, as a matter of law. Accordingly, Plaintiff's Motion for Partial Summary Judgment (Doc. # 64) is SUSTAINED in regard to its request for a declaratory judgment of non-infringement as to both patents (Count Three) and in regard to the Defendant's Counterclaims, and OVERRULED in regard to its request for a declaratory judgment of invalidity and unenforceability as to the Defendant's patents (Count Three). Concomitantly, Defendant's Motion for Partial Summary Judgment (Doc. # 61) is OVERRULED in regard to both of its Counterclaims and in regard to the Plaintiff's request for a declaratory judgment of non-infringement (Count Three). Finally, in view of the hearing held by this Court on March 1, 1996, in regard to the parties' motions for summary judgment, Plaintiff's Motion for a Hearing (Doc. # 62) on the Defendant's Motion for Partial Summary Judgment (Doc. [*9] # 61) is SUSTAINED, nunc pro tunc March 1, 1996.

Having summarized its conclusions regarding the parties' motions for summary judgment, this Court will now set forth the proper standard for summary judgment, a brief statement of background facts, the relevant law, and the specific reasons for its conclusions. This Court will then turn to the parties' discovery-related motions.

I. Summary Judgment Standard

Before focusing on the merits of the motions, the Court will set forth the relative burdens of the parties once a motion for summary judgment is made. Summary judgment must be entered "against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex Corp. v. Catrett, 477 U.S. 317, 322, 91 L. Ed. 2d 265, 106 S. Ct. 2548 (1986).*

Of course, [the moving party] always bears the initial responsibility of informing the district court of the basis for its motion, and identifying those portions of "the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, [*10] " which it believes demonstrate the absence of a genuine issue of material fact.

Id. at 323. See also *Boretti v. Wiscomb, 930 F.2d 1150, 1156 (6th Cir. 1991)* (The moving party has the "burden of showing that the pleadings, depositions, answers to interrogatories, admissions and affidavits in the record, construed favorably to the non-moving party, do not raise a genuine issue of material fact for trial." quoting *Gutierrez v. Lynch, 826 F.2d 1534, 1536* [6th Cir. 1987]). The burden then shifts to the non-moving party who "must set forth specific facts showing that there is a genuine issue for trial." *Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 250, 91 L. Ed. 2d 202, 106 S. Ct. 2505 (1986)* (quoting Fed.R.Civ.P. 56(e)). Thus, "once the moving party has met its initial burden, the nonmoving party must present evidence that creates a genuine issue of material fact making it necessary to resolve the difference at trial." *Talley v. Bravo Pitino Restaurant, Ltd., 61 F.3d 1241, 1245 (6th Cir. 1995).* Read together, Liberty Lobby and Celotex stand for the proposition that a party may move for [*11] summary judgment by demonstrating that the opposing party will not be able to produce sufficient evidence at trial to withstand a

directed verdict motion (now known as a motion for judgment as a matter of law. Fed.R.Civ.P. 50). *Street v. J.C. Bradford & Co., 886 F.2d 1472, 1478 (6th Cir. 1989).*

Once the burden of production has so shifted, the party opposing summary judgment cannot rest on its pleadings or merely reassert its previous allegations. It is not sufficient to "simply show that there is some metaphysical doubt as to the material facts." *Matsushita Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 586, 89 L. Ed. 2d 538, 106 S. Ct. 1348 (1986).* Rather, Rule 56(e) "requires the non-moving party to go beyond the [unverified] pleadings" and present some type of evidentiary material in support of its position. *Celotex Corp., 477 U.S. at 324.* Summary judgment "shall be rendered forthwith if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter [*12] of law." Fed.R.Civ.P. 56(c). Summary judgment shall be denied "if there are ... 'genuine factual issues that properly can be resolved only by a finder of fact because they may reasonably be resolved in favor of either party.'" *Hancock v. Dodson, 958 F.2d 1367, 1374 (6th Cir. 1992).* Of course, in determining whether a genuine issue of material fact exists, a court must assume as true the evidence of the nonmoving party and draw all reasonable inferences in the favor of that party. *Anderson, 477 U.S. at 255* (emphasis added). If the parties present conflicting evidence, a court may not decide which evidence to believe, by determining which parties' affiants are more credible; rather, credibility determinations must be left to the fact-finder. 10A Wright, Miller & Kane, Federal Practice and Procedure, § 2726. In ruling on a motion for summary judgment (in other words, in determining whether there is a genuine issue of material fact), "[a] district court is not ... obligated to wade through and search the entire record for some specific facts that might support the nonmoving party's claim." *Interroyal Corp. v. Sponseller, 889 F.2d 108, 111 (6th Cir. 1989),* [*13] cert. denied, *494 U.S. 1091, 108 L. Ed. 2d 967, 110 S. Ct. 1839 (1990).* See also, *L.S. Heath & Son, Inc. v. AT&T Information Systems, Inc., 9 F.3d 561, 1993 U.S. App. LEXIS 26670* (7th Cir. October 12, 1993); *Skotak v. Tenneco Resins, Inc., 953 F.2d 909, 915 n. 7* (5th Cir.), cert. denied, *506 U.S. 832, 113 S. Ct. 98, 121 L. Ed. 2d 59 (1992)* ("Rule 56 does not impose upon the district court a duty to sift through the record in search of evidence to support a party's opposition to summary judgment ...."). Thus, a court is entitled to rely, in determining whether a genuine issue of material fact exists on a particular issue, only upon those portions of the verified pleadings, depositions, answers to interrogatories and admissions on file, together with any affidavits submitted, specifically called to its attention by the parties.

II. Background Facts n3

n3 This Court declines to grant Plaintiff's request that this Court deny Defendant's Motion (Doc. # 61) merely because the factual narrative in that motion was not fully supported by authenticating documents, as required by Rule 56. The following narrative is taken from both parties' motions and does not include any facts disputed by the parties.

[*14]

This case involves two patents held by Defendant Sashco. United States Patent No. *4,776,458* (" *'458* patent") was awarded on October 11, 1988, and describes a transparent container ("cartridge") which dispenses a substantially transparent caulking compound by means of a moveable piston. United States Patent No. *4,863,014* (" *'014* patent") was awarded on September 5, 1989, and describes a transparent container ("squeeze tube") with a flexible sidewall which allows for manual dispensation of a transparent caulking compound and which has a region of reduced thickness so that the appearance of the substrate n4 surface may be previewed before application. These patents are described in further detail below.

n4 "Substrate" is synonymous with "substratum," which is defined as "something that is laid or spread under or that underlies and supports or forms a base for something else." Webster's Third New International Dictionary 2280 (unabridged 1976). This Court assumes that the parties are using the term "substrate" to mean a surface upon which the caulking compound is applied.

[*15]

In 1990, a company known as Dap, Inc. ("Old Dap"), which was a wholly-owned subsidiary of USG Corporation ("USG"), began selling a clear, rubber-based compound in a clear cartridge and squeeze tube (Doc. # 64, p.4-5). Sashco subsequently sued Old Dap in a Colorado federal court for infringement of its patents (Doc. # 61, Exh. E). Two relevant events occurred during this litigation. First, Old Dap changed the design of its cartridge to include a non-transparent portion, or mask, around fifty-eight percent of the cartridge's

circumference. No change was made to the tube. Sashco did not drop its claim with respect to the cartridge (Doc. # 64, p.5). Second, on September 20, 1991, USG sold Old Dap's assets to Wassall, Acquisitions, Inc., which promptly renamed the company "Dap Products, Inc." (Doc. # 64, p.5-6; Doc. # 61, Exh. G, p.3). Present Plaintiff Dap Products, Inc., continued Old Dap's business without interruption (Doc. # 64, p.6).

The litigation against Old Dap was resolved on August 20, 1992, by means of a consent decree (Doc. # 61, Exh. E). However, Sashco's subsequent attempt to enjoin present Plaintiff Dap from selling the products at issue in this lawsuit was unsuccessful, [*16] due to the Colorado court's ruling that Plaintiff was a new, unrelated entity and therefore not bound by the consent decree which resulted from the Colorado litigation (Doc. # 64, p.6 n.17). n5 This lawsuit followed.

n5 This Court notes that the Defendant has not raised the issue of collateral estoppel, which protects a party against whom a claim is asserted "from the burden of litigating an issue that has been fully and fairly tried in a prior action and decided against" the party bringing the claim. *Comair Rotron, Inc. v. Nippon Densan Corp., 49 F.3d 1535, 1537 (Fed. Cir. 1995)* (citing *Blonder-Tongue Laboratories, Inc. v. Univ. of Illinois Foundation, 402 U.S. 313, 28 L. Ed. 2d 788, 91 S. Ct. 1434 (1971))*. In order to assert collateral estoppel, the Defendant would have to "show that in the prior action the [Plaintiff] had a full and fair opportunity to litigate the issue; the issue was actually litigated; the controlling facts and applicable legal rules were the same in both actions; resolution of the particular issue was essential to the final judgment in the first action; and the identical issue was decided in the first action." Id. (citations omitted). In this case, the Plaintiff was not a party to the previous litigation and therefore did not have a full and fair opportunity to litigate the issue of infringement, and, the litigation having ended in a consent decree, that issue was not actually litigated and decided. Accordingly, principles of collateral estoppel are not applicable to this case.

[*17]

A. The *'458* Patent (Cartridge)

Sashco filed its original patent application for its cartridge on August 11, 1986. This application contained 29 claims. The first 21 claims were subsequently withdrawn from consideration. Claim 22, which was later redesignated as Claim 1 and is the only independent claim in the patent, was rejected on October 6, 1987, on the ground of obviousness. In a subsequent interview with Sashco's counsel on December 11, 1987, however, the Patent Examiner indicated that the claim "may be allowable if the motivation and the advantage of placing transparent caulk in a transparent container is set forth in the claim other than for viewing contents purposes." (Doc. # 64, Exh. F). Sashco amended the Claim accordingly on April 8, 1988, and filed a supplemental amendment on June 10, 1988. The final text of Claim 1 reads as follows:

A product for use in the building industry, comprising a cartridge formed as an elongated tubular housing having a longitudinal axis and surrounding sidewall fabricated of a transparent material, said housing having a hollow interior, a nozzle member enclosing a downstream end of said cartridge, a substantially transparent caulking [*18] compound contained in said cartridge, said caulking compound adapted to be placed on a substrate, and a piston member slideably received in the interior of said cartridge and enclosing an upstream end thereof so that the piston member may be pressed against the caulking compound to force the caulking compound out of said nozzle member as said piston member is moved downstream through said housing to dispense said caulking material onto said substrate whereby the combination of said housing and said caulking compound is substantially transparent in the transverse direction so as to allow a user to see completely through the surrounding sidewall and through the caulking compound from one side of the cartridge to the other whereby the substrate may be viewed through the combination of the housing and the caulking material placed therein so that the appearance of the substrate as affected by the caulking material may be seen prior to application of the caulking material and whereby the position of the piston member may be viewed as the caulking material is dispensed from the housing.

'458 patent, Claim 1 (emphasis added).

B. The *'014* Patent.

Defendant Sashco [*19] filed a patent application for its squeeze tube on October 7, 1988. This application was granted as filed on September 5, 1989. Claim 1, which is the only independent claim, reads as follows:

A product for the building industry, comprising an elongated container having a longitudinal axis and an interior, said container including a surrounding sidewall, a first closure forming a downstream end of container and a second closure forming an upstream end of the container, a dispensing nozzle extending outwardly from

said container at the downstream end thereof and having a flow passageway in fluid communication with the interior, and a substantially transparent caulking compound contained in the interior of the container, said sidewall being fabricated out of a flexible material whereby the container may be manually squeezed to dispense the caulking compound as an applied bead out of the dispensing nozzle and onto a selected substrate surface, said container having a region of reduced thickness in a direction transverse to the longitudinal axis longitudinally adjacent the upstream end of the container so that the caulking compound in the region of reduced thickness has a substantially [*20] uniform, flattened configuration and wherein said sidewall has facing sidewall portions on opposite sides of said region of reduced thickness that are fabricated of substantially transparent material whereby the substrate surface may be viewed through the combination of the facing sidewall portions and the caulking material therebetween so that the appearance of the substrate surface as affected by the caulking material may be seen prior to the application of the caulking material.

'014 patent, Claim 1 (emphasis added). In 1993, one of Sashco's competitors filed a request for re-examination which was described by the Patent Examiner as raising a "substantial new question" as to the patentability of this patent's claims and which cited, inter alia, a patent of a clear sealant in a flexible squeeze tube (Doc. # 64, Exh. L). Upon reexamination, the Patent Examiner confirmed Sashco's patent upon the following grounds:

The combination of the transparent caulking compound contained in a transparent type of squeezeable container is old and conventional as clearly evidenced by the references. However, none of the prior art fairly teaches or suggests the combination as [*21] a whole that a transparent type of squeezeable container including transparent caulking compound in a region of a reduced thickness in the transverse direction of the container so that the appearance of a substrate as affected by the caulking material may be seen prior to the application of the caulking material. Such limitation is clearly defined in [Claim 1].... The above mentioned features and their functions are not demonstrated by the prior art.

Remarks of Patent Examiner upon Reexamination, Doc. # 64, Exh. I (emphasis added).

Having reviewed the pertinent background facts, this Court now turns to its analysis of Defendant's Counterclaims for infringement (Doc. # 29) and Plaintiff's requests for a declaratory judgment as to non-infringement, invalidity and unenforceability (Doc. # 1).

III. Infringement

As noted above, Plaintiff sues for a declaratory judgment of non-infringement of the Defendant's patents, and Defendant has counterclaimed for infringement in violation of *35 U.S.C. § 271*. Both parties have moved for summary judgment on these claims. After setting forth the general law regarding patent infringement, this Court [*22] will turn to the specific patents and products at issue in this litigation. n6

n6 In regard to Plaintiff's Advice to the Court Regarding Submission of Sashco Commercial Products (Doc. # 86), this Court notes that it requested these products during a recent telephone conference between Court and counsel for the sole purpose of making certain that it understood the parties' descriptions of the Defendant's products. Although it should be apparent from the reasoning set forth in this opinion, the Court emphasizes that its examination of the Defendant's products played absolutely no role in its analysis of the infringement claims at issue in this lawsuit.

A. Law on Infringement

In determining whether the Plaintiff's products infringe the Defendant's patents, this Court must engage in a two-fold inquiry.

First, this Court must determine the meaning and scope of the patent claims asserted to be infringed. *Markman v. Westview Instr. Inc., 52 F.3d 967, 976 (Fed. Cir. 1995)*, aff'd *517 U.S. 370, 116 S. Ct. 1384, 134 L. Ed. 2d 577 (1996)*. [*23] This inquiry, which includes the construction of disputed terms of art contained within the relevant claims, is a question of law exclusively within the province of the court. *Markman, 116 S. Ct. at 1384.*

Second, the finder of fact must compare the properly construed claims to the device which is alleged to infringe, to determine whether infringement occurred. *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 1269-70 (Fed. Cir. 1986)*, cert. denied, *479 U.S. 1030, 93 L. Ed. 2d 829, 107 S. Ct. 875 (1987)*.

In regard to the first inquiry (claim construction), this Court may refer to four distinct sources to determine the meaning of claims: the claims themselves, the specification, the prosecution history, and extrinsic evidence. *Markman, 52 F.3d at 979.* The Federal Circuit recently provided a useful elaboration of the latter three categories, as follows:

[Specification]. The specification contains a written description of the invention that must enable one of ordinary skill in the art to make and use the invention. For claim construction purposes, the description may act as a sort of dictionary, which explains [*24] the invention and may define terms used in the claims. As we have often stated, a patentee is free to be his own lexicographer. The caveat is that any special definition given to a word must be clearly defined in the specification. The... specification itself does not delimit the right to exclude. That is the function and purpose of claims.

[Prosecution history]. This "undisputed public record" of proceedings in the Patent and Trademark Office is of primary significance in understanding the claims. The court has broad power to look as a matter of law to the prosecution history of the patent in order to ascertain the true meaning of language used in the patent claims. Although the prosecution history can and should be used to understand the language used in the claims, it too cannot "enlarge, diminish, or vary" the limitations in the claims.

[Extrinsic evidence]. Extrinsic evidence consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises. This evidence may be helpful to explain scientific principles, the meaning of technical terms, and terms of art that appear in the patent and prosecution [*25] history.

Extrinsic evidence is to be used for the court's understanding of the patent, not for the purpose of varying or contradicting the terms of the claims. When, after considering the extrinsic evidence, the court finally arrives at an understanding of the language as used in the patent and prosecution history, the court must then pronounce as a matter of law the meaning of that language.

Markman, 52 F.3d at 980-81 (citations omitted).

In addition to the above guidelines, it is important to note that "dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed." *Wahpeton Canvas Co. v. Frontier, Inc., 870 F.2d 1546, 1553 (Fed. Cir. 1989).* Furthermore, "if an express claim limitation is absent from the accused product, there can be no literal infringement as a matter of law." *Wolverine World Wide, Inc. v. Nike, Inc., 38 F.3d 1192, 1199 (Fed. Cir. 1994)* (citation omitted). Therefore, Plaintiff's cartridge can only infringe Patent 458 if it contains every express limitation contained in Claim 1 (the only independent claim) of that patent; similarly, Plaintiff's [*26] squeeze tube can only infringe Patent 014 if it contains every express limitation contained in Claim 1 (the only independent claim) of that patent.

With the above principles in mind, this Court now turns to its analysis of each of the Defendant's patents.

B. Infringement of the *'458* Patent

1. Claim Construction

The first step in the analysis is to determine, as a matter of law, the meaning and scope of the patent claims. As described above, Defendant Sashco's *'458* patent is directed to a substantially transparent combination of a cartridge and compound. The only independent claim in the patent emphasizes that this combination "is substantially transparent in the transverse direction so as to allow a user to see completely through... from one side of the cartridge to the other." This Court must now determine whether this claim, when properly construed, is limited to situations wherein a user can see through the center of the cartridge, as argued by the Plaintiff, or whether it encompasses situations in which a user can see completely through any other portion of the cartridge's sidewall, which is the construction urged by the Defendant. n7

n7 For example, Defendant attached pictures to its Motion for Partial Summary Judgment which showed that one can view through the Plaintiff's product and see a colored line which is taped to the wall behind the cartridge (Doc. # 61, Exh. J). One cannot, however, view the colored line through the center of the cartridge; instead, the line can only be seen through less than half of the right side of the cartridge.

[*27]

Before turning to extrinsic evidence and the prosecution history of the patent, this Court must first address a problematic aspect of the above-quoted language. This claim describes a cylindrical cartridge n8 that is substantially transparent in the transverse direction so that a user may see from one "side" of the cartridge to the other. Since this description apparently refers to a "circular cylinder"--that is, to a cylinder whose bases are circles, Webster's New World Dictionary of Mathematics 31 (1989)--it is most helpful to think about this description in terms of circles.

n8 The specification describes the container as consisting of "a tubular housing having first and second closing structures at opposite ends."

The term "tube" is defined as "a hollow, elongated, usually cylindrical body." Webster's Third New International Dictionary 2459 (unabridged 1976).

Unfortunately, however, a circle has no "sides." Unlike other geometrical figures which are defined in terms of the number of sides they possess [*28] n9 and their relation to each other, n10 a circle is defined as "a plane curve consisting of all points at a given distance from a given point." Webster's New World Dictionary of Mathematics 30 (1989). Moreover, the term "side" is defined as "the bounding line of a geometrical figure," Webster's Third New International Dictionary 2111 (unabridged 1976), and in ordinary Euclidean geometry a "line" is conceived of as being straight and of unlimited extent. Webster's New World Dictionary of Mathematics, 156-57 (1989). Therefore, the claim's reference to seeing "from one side of the cartridge to the other" is less helpful than might initially be supposed. n11 Accordingly, this Court's analysis will focus instead upon the meaning of the phrase "substantially transparent in the transverse direction."

n9 A polygon is defined as "a closed path of connecting line segments AB, BC,.... [which are termed] the sides of the polygon." Webster's New World Dictionary of Mathematics 200 (1989). Polygons are named according to the number of their sides: a triangle has three sides; a quadrilateral, four; a pentagon, five, and so on. Id. [*29]

n10 For example, quadrilaterals, which are four-sided polygons, are classified by the parallelism of their sides: "the figure is a trapezium, trapezoid, or parallelogram depending upon whether no, one, or two pairs of opposite sides are parallel, respectively. A rectangle is a parallelogram with all angles equal, and a square is a rectangle with all sides equal." Webster's New World Dictionary of Mathematics 218-19 (1989).

n11 Having demonstrated that the term "side" is a misnomer when used in reference to a circular cylinder, this Court will nevertheless observe that the expression "from one side to the other" clearly describes a point opposite the point of origin. Therefore, had this Court relied upon this expression to construe the claim, it would have concluded that this phrase indicates that a user must be able to see through the center of the cartridge to the opposite point of the cartridge, as opposed to merely being able to view a point which is an infinitesimal distance away.

Relying upon its authority to look to extrinsic evidence for assistance in construing the meaning [*30] of this claim, this Court will turn first to the dictionary. The definition of "transverse" is "extended or lying across or in a crosswise direction." Webster's Third New International Dictionary 2431 (unabridged 1976). The term "across" is defined as "to or on the opposite side." Id. at 20. Although this might appear merely to bring this Court to its earlier observation that a cylindrical cartridge does not have sides, the term "opposite" is a useful addition, suggesting that a user must see through the central longitudinal axis n12 of the cartridge in order to view the opposite point (rather than side) of the cartridge, exactly one hundred and eighty degrees on the circle from the initial point. n13

n12 The term "central longitudinal axis" is arguably a redundancy, as the term "axis" refers to "a straight line about which a body or three-dimensional figure rotates or may be supposed to rotate." Webster's Third New International Dictionary 153 (unabridged 1976). Presumably, therefore, the Defendant's cylindrical cartridge has only one longitudinal axis, located in the center of the cartridge. However, given that the parties have disputed this point, this Court will employ the term "central longitudinal axis" for purposes of clarity. [*31]

n13 Of course, given that the object discussed here is a three-dimensional cylinder rather than a two-dimensional circle, the user need not confine himself to looking directly across the cartridge in order to view "in the transverse direction," but may also look toward any point directly above or below the opposite point on the cartridge. The common denominator is that the user must look through the central longitudinal axis in order to view any of these points.

This initial conclusion is buttressed by a further observation. Given that a circle (and thus a cylindrical cartridge) has no sides, there are only two possible ways to construe the phrase "in the transverse direction": either it describes a direction extending toward the opposite point of the cartridge, exactly one hundred and eighty degrees on the circle from the initial point, or it describes a direction extending toward any point of the cartridge, including a point just an infinitesimal distance away. The

first construction appears to be the most logical choice, for two reasons.

First, the phrase "in the transverse [*32] direction" appears to refer to a particular, measurable direction, as opposed to any of numerous possible directions which would intersect any point of the cartridge, including points just an infinitesimal distance away. If this were not the case, the patent could have simply used the term "in any direction and for any distance."

Second, the latter construction, somewhat incongruously, would allow the Defendant's patent to encompass any cartridge which is substantially non-transparent, but which has a viewing window large enough to permit the user to see "through" the cartridge to any other point on the cartridge. This construction is belied by both the prosecution history and the claim itself. As discussed earlier, the Patent Examiner initially rejected Claim 1 for obviousness but later indicated that it "may be allowable if the motivation and the advantage of placing transparent caulk in a transparent container is set forth in the claim other than for viewing contents purposes." Defendant Sashco amended its claim accordingly to reflect the following advantages realized by its product:

> the substrate may be viewed through the combination of the housing and the caulking [*33] material placed therein so that the appearance of the substrate as affected by the caulking material may be seen prior to application of the caulking material and [] the position of the piston member may be viewed as the caulking material is dispensed from the housing.

'458 patent, Claim 1. These advantages--allowing the substrate, as it will be affected by the caulking material, to be viewed prior to applying that caulking material, and viewing the piston as the material is applied--would appear to require more transparency than that which can be provided by a viewing window, which may or may not allow one to directly "line up" the cartridge with the surface of the item to which the caulking compound is to be applied, so as to enable one to see how that surface will look once that compound is so applied. In any event, given the prosecution history described above, there must be some appreciable difference between Defendant Sashco's product and a product which merely allows the user to view the contents. Accordingly, this Court will not construe this Claim as encompassing all substantially non-transparent cartridges which have a large viewing window.

For the foregoing [*34] reasons, this Court will interpret the phrase "in the transverse direction" to mean toward the opposite point of the cartridge (i.e. one-hundred and eighty degrees from the initial point), and toward all points which are directly above and below that point. This construction necessarily limits the patent to situations wherein the user may view directly through the central longitudinal axis of the cartridge. n14

> n14 This Court notes here that it has reviewed the deposition testimony of Plaintiff's expert, Richard Killworth, which was cited by the Defendant in its Motion (Doc. # 61) and which discusses the interpretation of both of the patents at issue here. This Court concludes that this testimony does not refute or undermine the Plaintiff's arguments.

There is another reason why this construction of the patent's claim must be the correct one. The claim emphasizes that the "substrate may be viewed through the combination of the housing and the caulking material placed therein so that the appearance of the substrate [*35] as affected by the caulking material may be seen prior to application of the caulking material." This result can only be achieved if a user is able to see the area directly beneath and below the nozzle (which extends from the very center of the top of the cartridge), away from the piston, because this is the area to which the caulking material will be applied. As a practical matter, therefore, a user who wishes to view the substrate through the cartridge (as opposed to looking directly at the substrate surface by angling his or her head), will position himself or herself at the opposite end of the cartridge, so that he or she is "lined up" with the nozzle. From this position, he or she must look through the central longitudinal axis of the cartridge so as to view the substrate to which the caulking material will be applied. Importantly, a mere ability to see through any other portion of the cartridge--which, of necessity, would put the viewer's line of sight at an angle with the substrate and the piston--would not allow one to view the area directly below the nozzle, which is the area of the substrate to which the caulking material will be applied. Thus, the claim's [*36] asserted function can only be realized if the user is able to view directly through the central longitudinal axis of the cartridge.

As a final matter, this Court notes that the claim's requirement that the "position of the piston member may be viewed as the caulking material is dispensed from the housing" can be fairly interpreted as supporting its construction of the patent's claim. In regard to this function, the crucial issue is whether a partial view of the edge of the piston (as is provided by the Plaintiff's cartridge, due to the existence of an opaque mask which obscures 58% of the cylinder) is sufficient to fulfill this function, or whether a view of more than fifty percent of

the piston member--which necessarily is only achievable if any existing mask obscures less than 50% of the cylinder, so that a user can view directly through the central longitudinal axis of the cartridge--is required.

The answer to this issue would appear to depend upon the physical configuration of the piston member. For example, if the piston member is merely a flat base, a failure to exert pressure directly in the center of the piston might cause the piston member to slide unevenly, thus requiring [*37] a view of more than half of the piston member in order to determine the precise extent of the unevenness and the resulting position of the piston member. If, however, the piston member is "cup-shaped in configuration so that it has a flat base plate [] which bears against caulking material," as is described in the Defendant's preferred embodiment, then the piston member should slide evenly, thereby allowing a user to be certain of the precise position of the entire piston member even if he or she has only a partial view of said piston.

Accordingly, this Court must inquire as to whether the Defendant's patent is necessarily limited to piston members which have cup-shaped configurations. In this regard, the Court notes that the only part of the patent which describes the piston member as having a "cup-shaped configuration" is the patent's description of the preferred embodiment. However, language in the patent which immediately precedes the claim clearly reflects the Defendant's intent not to limit its patent to the description of its preferred embodiment:

> The present invention has been described with some degree of particularity directed to the preferred embodiment [*38] of the present invention. It should be appreciated, though, that the present invention is defined by the following claims construed in light of the prior art so that modifications or changes may be made to the preferred embodiment of the present invention without departing from the inventive concepts contained herein.

Moreover, the Federal Circuit has "cautioned against limiting the claimed invention to preferred embodiments or specific examples in the specification." *Texas Instr. v. United States Int'l Trade Comm'n, 805 F.2d 1558, 1563 (Fed. Cir. 1986);* accord *Laitram Corp. v. Cambridge Wire Cloth Co., 863 F.2d 855, 865 (Fed. Cir. 1988)* ("References to a preferred embodiment, such as those often present in a specification, are not claim limitations"), cert. denied, *490 U.S. 1068, 104 L. Ed. 2d 634, 109 S. Ct. 2069 (1989).* Therefore, this Court will not construe the Defendant's patent as being limited to piston members with cup-shaped configurations. Instead, this Court will construe the patent as encompassing other possible configurations of the piston member, including a flat base which may slide unevenly if pressure is not [*39] applied to the direct center of the piston member. In such a case, the user's need to view more than half of the piston member in order to determine the precise extent of the unevenness and the resulting position of the piston member, supports this Court's construction of the Defendant's claim to be limited to situations wherein the user may view directly through the central longitudinal axis of the cartridge.

2. Comparison of Claim 1 to Plaintiff's Cartridge

The next step in the analysis is to compare the properly construed claim to the product which is alleged to infringe the patent, in order to determine whether infringement has occurred. Although this is a factual question, this Court may, upon a motion for summary judgment, determine whether there exists any genuine issue of material fact on this issue.

This Court has held that the Defendant's patent is limited to situations wherein a user can view directly through the central longitudinal axis of the cartridge, toward the opposite point and/or points above and below that point. Here, it is undisputed that the Plaintiff's product contains a mask which obscures approximately 58% of the cartridge. Given this limitation, no [*40] reasonable jury could conclude that a user could view directly through the central longitudinal axis of the Plaintiff's cartridge, as there is no point on the cartridge from which a user could look through to a point one-hundred and eighty degrees away without viewing the opaque mask. n15 In short, it would be a physical impossibility for a user to have a line of sight such as to be able to view both how the surface to which the caulking compound will be applied will be affected, and the position of the piston member. Therefore, this Court finds that there exists no genuine issue of material fact as to this question, and instead holds as a matter of law that the Plaintiff's product does not infringe Defendant Sashco's *'458* patent. n16

n15 Although this Court can look through the opaque mask and discern the outline and color of objects which are placed next to the mask, this does not satisfy the patent's requirement that "the combination of said housing and said caulking compound is substantially transparent in the transverse direction so as to allow a user to see completely through the surrounding sidewall...." (Patent *'458*, Claim 1). The term "transparent" is defined as "having the property of transmitting light without appreciable scattering so that bodies lying beyond are entirely visible." Webster's Third New International Dictionary 2430 (unabridged 1976).

In contrast, the term "translucent" is defined as "admitting and diffusing light so that objects beyond cannot be clearly distinguished: partly transparent." Id. at 2429. [*41]

n16 Under the doctrine of equivalents, infringement may be found where the patent holder "show[s] the presence of every element [of a claim] or its substantial equivalent in the accused device." *Pennwalt Corp. v. Durand-Wayland, Inc., 833 F.2d 931, 935 (Fed. Cir. 1987),* cert. denied, *485 U.S. 961, 99 L. Ed. 2d 426, 108 S. Ct. 1226 (1988).* Due to the parties' failure to raise, argue or brief the doctrine of equivalents, this Court will not reach the issue of whether the Plaintiff's products infringe Defendant Sashco's patents under this doctrine, and will rule only that there is no literal infringement of the patents. Although mindful of the Federal Circuit's statement that "the trial judge does not have discretion to choose whether to apply the doctrine of equivalents when the record shows no literal infringement," *Hilton Davis Chem. Co. v. Warner-Jenkinson Co., Inc., 62 F.3d 1512, 1522 (Fed. Cir. 1995),* cert. granted, *116 S. Ct. 1014 (1996),* and the resulting implication that courts must consider the doctrine of equivalents, this Court does not believe that the Federal Circuit would require trial courts to apply the doctrine where it is not raised or argued by the parties themselves.

In any event, if this Court were to reach the issue, it would hold merely that summary judgment for the Plaintiff is proper because the Defendant, which bears the burden of proof on the issue at trial, has failed to create a genuine issue of material fact as to whether the Plaintiff's products infringe under the doctrine of equivalents. See *Intellicall, Inc. v. Phonometrics, Inc., 952 F.2d 1384, 1389 (Fed. Cir. 1992)* (affirming grant of summary judgment to the plaintiff where the defendant, a non-movant on the non-infringement issue, failed to provide evidence of a necessary element of the doctrine of equivalents).

[*42]

Accordingly, Plaintiff's Motion for Partial Summary Judgment (Doc. # 64) is SUSTAINED both as to that portion of Count Three which requests a declaration of non-infringement of the Defendant's *'458* patent, and as to Counterclaim One. Conversely, Defendant's Motion for Partial Summary Judgment (Doc. # 61) is OVERRULED both as to Counterclaim One, and as to that portion of Count Three which requests a declaration of non-infringement of the Defendant's *'458* patent.

C. Infringement of the *'014* Patent

1. Claim Construction

This Court now turns to Defendant Sashco's *'014* patent, which describes a transparent squeeze tube that has a region of reduced thickness which allows the substrate to be viewed prior to application of the compound. The specific portion of Claim 1, the only independent claim, implicated in this case is the statement that "the compound in the region of reduced thickness has a substantially uniform, flattened configuration." Plaintiff argues that this requirement does not encompass its product, which is best described as a toothpaste-type squeeze tube. Defendant argues that its patent does extend to toothpaste-type tubes, similar to the product marketed by the Plaintiff. [*43]

As before, this Court will use the dictionary as a starting point for its analysis, focusing on the requirement that the caulking compound in the specified region have a "substantially uniform, flattened configuration." The term "flat" is defined as "having or marked by a continuous surface that is horizontal or nearly so without significant curvature or inclination." Webster's Third New International Dictionary 865 (unabridged 1976). The term "flattened" means "reduced to an even or more nearly even surface." Id. at 867. Therefore, a straightforward interpretation of this claim requires the slope or inclination of the tube to be noticeably reduced in this particular region, so that the surface of the tube (and the compound within it) becomes more horizontal and even. Accordingly, a toothpaste tube which does not have an appreciably "flattened" region, but which merely has an unchanging, tapered slope from one end of the tube to the other, will not fall within this patent's definition.

This interpretation of "flattened" is supported by specific language in the patent's specification, which describes this region as "a packet of caulking compound [having] a uniform [*44] dimensional thickness to facilitate preview of the caulking compound... [which] may be generally a rectangular pillow of caulking material... [which] allows the transparent facing sidewall portions to be oriented substantially parallel to one another to reduce distortion when the substrate surface is viewed." See also Figure 2 (demonstrating that letters of words may be viewed through this region of the product without significant distortion). These descriptions, taken either separately or together, indicate that the region of reduced thickness described in the patent is indeed intended to be "flattened" by having less of a slope (and, ideally, no slope) than the remainder of the tube. Simply put, these descriptions do not describe a toothpaste tube.

Bearing this construction in mind, this Court now turns to an examination of the Plaintiff's tube to determine if there exists a genuine issue of material fact as to whether this product infringes the Defendant's patent.

2. Comparison of Claim 1 to Plaintiff's Squeeze Tube

As before, the next step in this Court's analysis is to compare the properly construed claim to the product which is alleged to infringe the [*45] patent, in order to determine whether infringement has occurred. Upon even a cursory examination of the Plaintiff's squeeze tube, it becomes quite clear that there is no flattened region at the end of the tube, as that term is understood and used within the context of Defendant Sashco's patent. n17 Instead, the Plaintiff's tube slopes from one end to the other. Therefore, since no reasonable jury could conclude that Plaintiff's tube contains the flattened region specified in the Defendant's patent, there exists no genuine issue of material fact as to the issue of whether Plaintiff's squeeze tube infringes Defendant's *'014* patent. Accordingly, Plaintiff's Motion for Partial Summary Judgment (Doc. # 64) is SUSTAINED both as to that portion of Count Three which requests a declaration of non-infringement of the Defendant's *'014* patent, and as to Counterclaim Two. Conversely, Defendant's Motion for Partial Summary Judgment (Doc. # 61) is OVERRULED both as to Counterclaim Two, and as to that portion of Count Three which requests a declaration of non-infringement of the Defendant's *'014* patent.

n17 For the record, this Court notes that the plastic strip at the very end of the tube--which contains no caulking compound and appears merely to serve the function of allowing the tube to be hung up in the store--is not the flattened region defined in the Defendant's patent.

[*46]

IV. Invalidity and Unenforceability

As noted above, Plaintiff sues for a declaratory judgment that the Defendant's patents are invalid and unenforceable, and has moved for summary judgment on this claim. Although this Court has now held, as matter of law, that the Plaintiff's products do not infringe the patents at issue in this lawsuit, the relevant case law indicates that this ruling does not automatically divest this Court of jurisdiction n18 over Plaintiff's claims of invalidity. After briefly setting forth this law, this Court will proceed to consider whether there exists a genuine issue of material fact as to these claims.

n18 The existence of this Court's jurisdiction in this context depends upon whether the litigants satisfy the case or controversy requirement of Article III of the United States Constitution. In upholding the constitutionality of the Declaratory Judgment Act, *28 U.S.C. § 2201*, the Supreme Court set forth the following principles relating to a court's jurisdiction under the Act:

> A "controversy" in this sense must be one that is appropriate for judicial determination. A justiciable controversy is thus distinguished from a difference or dispute of a hypothetical or abstract character.... The controversy must be definite and concrete, touching the legal relations of parties having adverse legal interests. It must be a real and substantial controversy admitting of specific relief through a decree of a conclusive character....
>
> *Aetna Life Ins. Co. v. Haworth, 300 U.S. 227, 240-41, 81 L. Ed. 617, 57 S. Ct. 461 (1937).*

[*47]

As a general matter, the Supreme Court has made clear its preference that in suits for patent infringement the district court inquire fully into the issue of the patent's validity. *Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 89 L. Ed. 1644, 65 S. Ct. 1143 (1945),* quoted with approval in *Cardinal Chemical Co. v. Morton Int'l, Inc., 508 U.S. 83, 113 S. Ct. 1967, 1977, 124 L. Ed. 2d 1 (1993).* Importantly, whether a district court retains jurisdiction to consider the issue of a patent's validity after it has determined that the patent at issue was not infringed, depends upon the manner in which the claim of invalidity was asserted. Where invalidity is asserted as an affirmative defense to the adverse party's claim of infringement, a finding of non-infringement automatically divests the court of jurisdiction to consider the issue of invalidity, due to the resolution of the claim. See *Deposit Guaranty Nat'l Bank v. Roper, 445 U.S. 326, 335 n.7, 63 L. Ed. 2d 427, 100 S. Ct. 1166 (1980)* (explaining that the district court "was incorrect to adjudge the patent valid after ruling that there had been no infringement" as this [*48] "decided a hypothetical controversy") (citing *Thomas & Betts Co. v. Electrical Fittings Corp., 23 F. Supp. 920 (S.D.N.Y. 1938)).* If, however, one of the parties has sought a declaratory judgment as to the validity or invalidity of the patent, a finding of non-infringement will not automatically resolve this separate claim. *Altvater v. Freeman, 319 U.S. 359, 363, 87 L. Ed. 1450, 63 S. Ct. 1115 (1943)* ("Though the decision of non-infringement

disposes of the bill and the answer, it does not dispose of the counterclaim which raises the question of validity.").

In this case, because Plaintiff Dap has brought a separate claim for a declaratory judgment of the invalidity and unenforceability of the Defendant's patents, this Court's finding of non-infringement of those patents does not automatically divest it of jurisdiction to consider the issue of invalidity. While there is an absence of any briefing by the parties as to the nature and extent of their interests in the sole remaining issue of invalidity, in view of the Supreme Court's strong preference that district courts "fully inquire" into the issue of invalidity, this Court will proceed to rule [*49] upon the Plaintiff's Motion for Partial Summary Judgment on that issue.

Accordingly, this Court now turns to the aforesaid motion to determine whether there exists a genuine issue of material fact as to the alleged invalidity and unenforceability of the Defendant's patents. After setting forth the applicable law, this Court will turn to the specific patents and products at issue here.

A. Law on Invalidity (Best Mode)

Under *35 U.S.C. § 282*, patents are presumed to be valid. Therefore, a party asserting invalidity must establish such a claim by clear and convincing evidence. *United States Gypsum Co. v. National Gypsum Co., 74 F.3d 1209, 1212 (Fed. Cir. 1996)*. A patent may be invalid if it fails to comply with the best mode requirement, which requires the specification to "set forth the best mode contemplated by the inventor of carrying out his invention." *35 U.S.C. § 112*.

It is well-settled that a best mode analysis has two elements. First, the fact-finder must engage in a subjective inquiry to determine whether the inventor "knew of a mode of practicing his invention at the time he filed his patent application [*50] which he considered to be better than any other." *In re Hayes Microcomputer Prod., Inc. Patent Litigation, 982 F.2d 1527, 1536 (Fed. Cir. 1992)* (citing *Chemcast Corp. v. Arco Indus. Corp., 913 F.2d 923, 927 (Fed. Cir. 1990)*). Second, if the inventor did have a best mode, the fact-finder must engage in an objective inquiry to determine "whether he disclosed it and did so adequately to enable one of ordinary skill in the art to practice the best mode." Id. These inquiries are treated as questions of fact. *Chemcast Corp., 913 F.2d at 928*.

Before this analysis can be applied, however, it is necessary to delimit the scope of the claimed invention. The Federal Circuit has clarified that the best mode requirement applies only to the claimed invention: "Unclaimed subject matter is not subject to the disclosure requirements of § 112; the reasons are pragmatic: the disclosure would be boundless, and the pitfalls endless." *Engel Indus., Inc. v. Lockformer Co., 946 F.2d 1528, 1531 (Fed. Cir. 1991)*. This principle was recently emphasized by the Federal Circuit in a best mode case involving a patented interferometer [*51] that was sold in an encasement not claimed in the patent:

> At least one of the inventors contributed to the commercial design. The failure to disclose the commercial mode, however, does not ipso facto result in a section 112 violation. The focus of a section 112 inquiry is not what a particular user decides to make and sell.... Rather, in keeping with the statutory mandate, our precedent is clear that the parameters of a section 112 inquiry are set by the CLAIMS.

Zygo Corp. v. Wyko Corp., 79 F.3d 1563, 1567 (Fed. Cir. 1996) (emphasis in original). n19 Because this issue depends upon an interpretation of the scope of the claims set forth in the patent, it is an issue for this Court to decide. See *Markman v. Westview Instr., Inc., 517 U.S. 370, 116 S. Ct. 1384, 1387, 134 L. Ed. 2d 577 (1996)* (holding that "the construction of a patent... is exclusively within the province of the court").

> n19 This Court notes here the similarity between this principle, which applies to purported best mode violations, and the principle that courts should decide whether infringement has occurred "by comparing the accused device with the claims in suit, not with a preferred or commercial embodiment of the patentee's claimed invention." *Martin v. Barber, 755 F.2d 1564, 1567 (Fed. Cir. 1985)*.

[*52]

B. Validity of Defendant's Patents

Plaintiff asserts that both of Defendant Sashco's patents are invalid because the inventor failed to disclose the best mode. In regard to the *'458* patent, Plaintiff argues that the inventor preferred to use compound from one particular company in its cartridge, but failed to disclose the name or source of this compound (Doc. # 64). In regard to the *'014* patent, Plaintiff claims that the Defendant manufactured its own compound for use in its squeeze tube, but failed to disclose the components and qualities of that product (Doc. # 64). As noted, before turning to the two-step analysis to determine whether there exists a genuine issue of material fact as to this claim, this Court must first discuss the scope of the Defendant's patents.

The pertinent issues in this initial inquiry are whether the Defendant's patents--which describe a

combination of a transparent cartridge or squeeze tube with transparent compound--required the inventor to disclose either the brand-name of the compound which he preferred to use in his cartridge, or the particular formulation of the compound which he preferred to use in his squeeze tube. On this point, the Federal [*53] Circuit has provided the following useful analysis:

A description of particular materials or sources or of a particular method or technique selected for manufacture may or may not be required as part of a best mode disclosure respecting a device. Thus, the particulars of making a prototype or even a commercial embodiment do not necessarily equate with the "best mode" of "carrying out" an invention. Indeed, the inventor's manufacturing materials or sources or techniques used to make a device may vary from wholly irrelevant to critical.

For example, if the inventor develops or knows of a particular method of making [his product] which substantially improves the operation or effectiveness of his invention, failure to disclose such peripheral development may well lead to invalidation. On the other hand, an inventor is not required to supply "production" specifications.... There is no mechanical rule that a best mode violation occurs because the inventor failed to disclose particular manufacturing procedures beyond the information sufficient for enablement.

One must look at the scope of the invention, the skill in the art, the evidence as to the inventor's belief, and all of the [*54] circumstances in order to evaluate whether the inventor's failure to disclose particulars of manufacture gives rise to an inference that he concealed information which one of ordinary skill in the art would not know.

Wahl Instr., Inc. v. Acvious, Inc., 950 F.2d 1575, 1580 (Fed. Cir. 1991). Furthermore, in discussing the "production specifications" exception to the best mode requirement, the Federal Circuit has stated that

the best mode requirement does not require an inventor to disclose production details so long as the means to carry out the invention are disclosed. This includes providing supplier/trade name information where it is not needed, i.e., where such information would be "mere surplusage--an addition to the generic description." Such supplier/trade name information must be provided only when a skilled artisan could not practice the best mode of the claimed invention absent this information.

Transco Procs. Inc. v. Performance Contracting, Inc., 38 F.3d 551, 560 (Fed. Cir. 1994), cert. denied, *513 U.S. 1151, 115 S. Ct. 1102, 130 L. Ed. 2d 1069 (1995)* (emphasis added).

These legal guidelines indicate [*55] that this Court must examine all of the factual circumstances in order to determine whether the use of a particular brand or formulation of compound either "substantially improved" the operation of Defendant's products or was a mere "production specification." Because some of these circumstances are in dispute (e.g., the inventor's state of mind), and because others have not yet been addressed by the parties (e.g., whether a skilled artisan could manufacture the cartridge without knowledge of a particular brand-name of compound), this inquiry cannot be resolved upon this motion for summary judgment. Therefore, Plaintiff's Motion for Partial Summary Judgment (Doc. # 64) is OVERRULED in regard to that portion of Count Three which requests a declaration of invalidity and unenforceability of Defendant's patents. n20

n20 This Court will make two points here. First, the Court notes for the record that the Defendant did not move for summary judgment in regard to that portion of Count Three of Plaintiff's Complaint which requests a declaration of invalidity and unenforceability of Defendant's patents.

Second, the Court notes that although the Supreme Court has not directly addressed the nature and extent of a district court's jurisdiction in a case such as this one--namely, where a plaintiff who is seeking declaratory judgments of non-infringement and invalidity has been awarded the former but not the latter upon a motion for summary judgment--it has pointed out that "the Declaratory Judgment Act affords the district court some discretion in determining whether or not to exercise that jurisdiction, even when it has been established." *Cardinal Chemical Co., 113 S. Ct. at 1974 n.17.* Therefore, even if the Plaintiff succeeds in establishing this Court's jurisdiction over the sole remaining issue of invalidity, the continuing viability of Plaintiff's request for a declaratory judgment as to the invalidity and unenforceability of the Defendant's patents is not assured.

[*56]

V. Remaining Discovery Motions

Having determined that the Plaintiff's products which are at issue in this litigation do not infringe either

of the Defendant's patents, this Court now turns to the discovery motions which are currently pending in this case. Because all of these motions deal exclusively with the issue of the Plaintiff's alleged infringement--which is no longer a viable issue in this litigation--they are all overruled as moot.

Three of the motions involve the Defendant's refusal to allow Mark Bross, who was the draftsman for the *'014* patent, to answer certain questions in his deposition regarding the interpretation and infringement of that patent. In light of this Court's ruling that Plaintiff's squeeze tube did not, as a matter of law, infringe this patent, these questions are no longer relevant to this litigation. Therefore, the following motions are OVERRULED as moot: Plaintiff's Motion to Compel Defendant's Expert Witness to answer certain deposition questions (Doc. # 66); Plaintiff's alternative Motion to Strike Mr. Bross as an Expert Witness (Doc. # 66); and Defendant's Motion for a Protective Order (Doc. # 72).

Similarly, the Plaintiff's failure to answer [*57] written interrogatories relating to the number of allegedly infringing sales of cartridges and squeeze tubes are no longer relevant, as these interrogatories go solely to the issue of damages for the alleged infringement, which are no longer an issue in this case. Accordingly, Defendant's Motion to Compel the Plaintiff to Answer Interrogatories (Doc. # 78) is OVERRULED as moot. For the same reasons, Plaintiff's Motion to Exclude Evidence of Defendant's New Damage Theories (Doc. # 74) is also OVERRULED as moot.

VI. Further Procedures to Resolve this Litigation

In a conference held between Court and counsel, it was suggested that the most logical next step in this litigation is to enter partial judgment for the Plaintiff on the issue of infringement under Rule 54(b), n21 so that the parties may appeal that issue before determining the nature and extent of their interests in going to trial on the issue of invalidity. During this conversation, Plaintiff's counsel indicated that his client's only interest in adjudicating the issue of invalidity, assuming that the Court's determination of non-infringement of both patents is upheld on appeal, is in future possibilities of redesigning [*58] its cartridge. This appears to the Court to be, at best, a hypothetical or academic interest. Moreover, both parties indicated that they believe they can settle the issue of invalidity amicably when the issue of infringement is resolved. Finally, allowing entry of judgment pursuant to Rule 54(b) would further the Court's interest in conserving judicial resources which might otherwise be expended on a trial ultimately regarded as unnecessary by both of the parties. For these reasons, this Court finds that there is no just reason for delay, and therefore ORDERS that judgment be entered for the Plaintiff and against the Defendant on the issue of infringement, pursuant to Rule 54(b). The Clerk of Courts is instructed to wait seven (7) days from the date of this decision before filing said judgment, in order to allow counsel to object to the entry of judgment pursuant to Rule 54(b).

n21 This Rule, which is captioned "Judgment Upon Multiple Claims or Involving Multiple Parties," reads as follows:

> When more than one claim for relief is presented in an action, whether as a claim, counterclaim, cross-claim, or third-party claim, or when multiple parties are involved, the court may direct the entry of a final judgment as to one or more but fewer than all of the claims or parties only upon an express determination that there is no just reason for delay and upon an express direction for the entry of judgment. In the absence of such determination and direction, any order or other form of decision, however designated, which adjudicates fewer than all the claims or the rights and liabilities of fewer than all the parties shall not terminate the action as to any of the claims or parties, and the order or other form of decision is subject to revision at any time before the entry of judgment adjudicating all the claims and the rights and liabilities of all the parties.
>
> Rule 54(b).

[*59]

WHEREFORE, based upon the aforesaid, Defendant's Motion for Partial Summary Judgment (Doc. # 61) is OVERRULED as to its Counterclaims and Count Three of Plaintiff's Complaint. The aforesaid Motion is OVERRULED as moot, without prejudice to renewal, in regard to Counts One and Two of Plaintiff's Complaint.

Plaintiff's Motion for a Hearing (Doc. # 62) on said motion (Doc. # 61) is SUSTAINED, nunc pro tunc March 1, 1996.

Plaintiff's Motion for Partial Summary Judgment (Doc. # 64) is OVERRULED in regard to its request in Count Three for a declaratory judgment of invalidity and unenforceability as to both patents. The aforesaid Motion is SUSTAINED in regard to its request for a declaratory judgment of non-infringement as to both patents.

The following motions are OVERRULED as moot: Plaintiff's Motion to Compel Defendant's Expert Witness to answer certain deposition questions (Doc. # 66); Plaintiff's alternative Motion to Strike Mr. Bross as an Expert Witness (Doc. # 66); Defendant's Motion for a Protective Order (Doc. # 72); Plaintiff's Motion to Exclude Evidence of Defendant's New Damage Theories (Doc. # 74); and Defendant's Motion to Compel the Plaintiff to Answer Interrogatories [*60] (Doc. # 78).

The parties are ORDERED to inform this Court, within three (3) days of the date of this decision, of the status and viability of Counts One and Two of the Plaintiff's Complaint.

A declaratory judgment of non-infringement of Defendant's *'458* patent and Defendant's *'014* patent is ORDERED to be entered, pursuant to Rule 54(b), in favor of the Plaintiff and against the Defendant, as there is no just reason for delay. The Clerk of Courts is instructed to wait seven (7) days from the date of this decision before filing said judgment, in order to allow counsel to object to the entry of judgment pursuant to Rule 54(b).

Judgment on the Defendant's Counterclaims is ORDERED to be entered, pursuant to Rule 54(b), in favor of the Plaintiff and against the Defendant, as there is no just reason for delay. The Clerk of Courts is instructed to wait seven (7) days from the date of this decision before filing said judgment, in order to allow counsel to object to the entry of judgment pursuant to Rule 54(b).

July 17, 1996

WALTER HERBERT RICE

UNITED STATES DISTRICT JUDGE

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DIXIE USA, INC., a Texas corporation, and BUCHBOARD PATIENT SHIFTERS, INC., a Texas corporation, Plaintiffs, v. INFAB CORPORATION, a Delaware corporation, and DONALD CUSICK, an individual, and PICKER INTERNATIONAL, INC., a New York corporation, Defendants

Case No. CV 89-4396 SVW

UNITED STATES DISTRICT COURT FOR THE CENTRAL DISTRICT OF CALIFORNIA

1990 U.S. Dist. LEXIS 15789; 16 U.S.P.Q.2D (BNA) 1392

February 15, 1990, Decided

February 26, 1990, Filed

CASE SUMMARY

PROCEDURAL POSTURE: Defendants filed a motion for summary judgment of non-infringement on the claims of patent infringement and inducing patent infringement.

OVERVIEW: Plaintiffs filed a patent infringement action against defendants. Plaintiffs argued that defendants' stretcher-type plastic board for carrying medical patients infringed plaintiffs' patent. Defendants argued that plaintiffs amended their patent claim regarding the handholds to overcome the prior art. Defendants claimed that this amendment, which narrowed plaintiffs' patent claim, estopped plaintiffs from recapturing what they gave up in obtaining their patent. The court agreed with defendants and estopped plaintiffs from arguing the doctrine of equivalents. The court balanced the equities and determined that application of prosecution history estoppel was appropriate because the equities did not tip in favor of plaintiffs.

OUTCOME: The court granted defendants' motion for summary judgment of non-infringement and dismissed plaintiffs' first two causes of action because no cause of action for infringement existed due to prosecution history estoppel.

CORE CONCEPTS

Civil Procedure : Summary Judgment : Burdens of Production & Proof
Civil Procedure : Summary Judgment : Summary Judgment Standard
Summary judgment is proper only where the pleadings, depositions, answers to interrogatories, and admission on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law. Fed. R. Civ. Proc. 56(c). The moving party has the burden of demonstrating the absence of a genuine issue of fact for trial.

Civil Procedure : Summary Judgment : Burdens of Production & Proof
A party opposing a properly supported motion for summary judgment must set forth specific facts showing that there is a genuine issue for trial. Fed. R. Civ. Proc. 56(e).

Patent Law : Infringement : Summary Judgment
Patent Law : Infringement : Prosecution History Estoppel
In the area of patent law, summary judgment will be upheld where the claims do not read on the accused structure to establish literal infringement and a prosecution history estoppel makes clear that no actual infringement under the doctrine of equivalents can be found.

Patent Law : Infringement : Doctrine of Equivalents

To prevail under the doctrine of equivalents, a plaintiff must show that the accused item performs substantially the same function in substantially the same way to obtain the same result.

Patent Law : Infringement : Doctrine of Equivalents
In applying the doctrine of equivalents, each limitation must be viewed in the context of the entire claim. It is well settled that each element of a claim is material and essential, and that in order for a court to find infringement, the plaintiff must show the presence of every element or its substantial equivalent in the accused device.

Patent Law : Infringement : Prosecution History Estoppel
The doctrine of prosecution history estoppel is an equitable tool for determining the permissible scope of patent claims as against a specific structure accused of infringement. Claim amendments and arguments made during the prosecution for a patent may preclude a patentee from recapturing what was foregone during prosecution of the patent application.

Patent Law : Infringement : Prosecution History Estoppel
The doctrine of prosecution history estoppel prevents a patentee from enforcing its claims against otherwise legally equivalent structures if those structures are excluded by claim limitations added in order to avoid prior art.

Patent Law : Infringement : Doctrine of Equivalents
Patent Law : Infringement : Prosecution History Estoppel
The invocation of the doctrine of prosecution history estoppel does not automatically preclude the application of the doctrine of equivalents. That a patent applicant narrows his claim to secure a patent does not always mean that prosecution history estoppel completely prohibits the patentee from recapturing some of what was originally claimed. The amount of coverage retained depends on the circumstances of each case.

Patent Law : Infringement : Doctrine of Equivalents
Patent Law : Infringement : Prosecution History Estoppel
Both the doctrine of equivalents and the doctrine of prosecution history estoppel are equitable in nature, and require courts to engage in a balancing analysis guided by equitable and public policy principles underlying the doctrines involved and by the facts of the particular case.

JUDGES:
[*1]

Stephen V. Wilson, United States District Judge.

OPINIONBY:
WILSON

OPINION:

MEMORANDUM OPINION AND ORDER GRANTING DEFENDANT'S MOTION FOR SUMMARY JUDGMENT OF NON-INFRINGEMENT

Plaintiffs' first amended complaint lists causes of action for patent Infringement, inducing patent infringement, unfair competition, and trademark infringement. Defendants Infab Corporation ("Infab"), Donald Cusick ("Cusick"), and Picker International ("Picker") now move for summary judgment of non-infringement on the claims of patent infringement and inducing patent infringement.

STATEMENT OF FACTS

Plaintiffs contend that Infab's stretcher-type plastic board for carrying medical patients infringes plaintiffs' Patent No. 4,067,079. Plaintiffs allege that Picker is a former distributor of plaintiffs' boards and that after the distributorship was terminated, Picker requested Cusick (president of Infab) to cause Infab to manufacture and sell to Picker copies of plaintiffs' patented board.

Plaintiffs' patent shows and describes a rectangular plastic board for carrying medical patients. The board has two kinds of openings adjacent to the periphery of the board. In the words of the patent, the board has

a plurality of openings in [*2] said slab and disposed adjacent the periphery of said support surface providing means for gripping the plastic slab to effect sliding movement of the plastic slab and the patient support thereon;

said plurality of openings comprising generally rectangular openings having rounded corners and rounded openings for grasping the slab for moving a patient;

said openings being disposed inwardly from the periphery of the slab a greater distance than the thickness of the slab.

The patent claim also states that a patient can be X-rayed through the board.

Defendants' accused board is also used for moving patients, is octagonal in shape, and allows for a patient to be X-rayed through the board. The accused board however, does not have any rounded openings; instead, all the openings are rectangular in shape.

STANDARD OF REVIEW

Summary judgment is proper only where "the pleadings, depositions, answers to interrogatories, and admission on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." Fed. R. Civ. Proc. 56(c). The moving party has the burden of demonstrating the absence [*3] of a genuine issue of fact for trial. *Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 256 (1986).* A party opposing a properly supported motion for summary judgment must set forth specific facts showing that there is a genuine issue for trial. Id.; Fed. R. Civ. Proc. 56(e).

In the area of patent law, "summary judgment will be upheld 'where the claims do not 'read on' the accused structure' to establish literal infringement 'and a prosecution history estoppel makes clear that no actual infringement under the doctrine of equivalents can be found.'" *Townsend Engineering Co. v. Hitec Co., Ltd., 829 F.2d 1086 (Fed. Cir. 1987)* (quoting *Brenner v. United States, 773 F.2d 306 (Fed. Cir. 1985);* see D. Chisum, 4 Patents 18.06[2] n.1 (1989).

DISCUSSION

A. The Doctrine of Equivalents

Plaintiffs concede that there is no literal infringement of their patent. Instead, they argue that the accused board is infringing their patent under the doctrine of equivalents. To prevail under the doctrine of equivalents, the plaintiffs must show that the accused item "performs substantially the same function in substantially the same way to obtain the same result." Mannesmann [*4] *Demag Corp. v. Engineered Metal Prod., 793 F.2d 1279, 1283-84 (Fed. Cir. 1986),* quoting *Graver Tank & Mfg. Co. v. Linde Air Products Co., 70 S. Ct. 854, 856 (1950).* Furthermore, "in applying the doctrine of equivalents, each limitation must be viewed in the context of the entire claim. ... It is ... well settled that each element of a claim is material and essential, and that in order for a court to find infringement, the plaintiff must show the presence of every element or its substantial equivalent in the accused device." *Pennwalt Corp. v. Durand-Wayland Inc., 833 F.2d 931, 935 (Fed. Cir. 1987)* (quoting *Perkin-Elmer Corp. v. Westinghouse Elec. Corp., 822 F.2d 1528 (Fed. Cir. 1987).*

In the case at bar, the Plaintiffs' patent has only one claim. Accordingly, the Plaintiffs must show the presence of every element or the substantial equivalent of every element of their patent claim in the Defendants' accused device. In comparing the accused board to the patented board, the boards are nearly identical except for the shape of the handholds. Plaintiffs naturally argue that defendants' rectangular handholds are substantially equivalent to the rectangular and round handholds [*5] on the patented device.

B. Prosecution History Estoppel

Defendants contend that the doctrine of prosecution history estoppel prevents the Plaintiffs from arguing the doctrine of equivalents. The doctrine of prosecution history estoppel is "an equitable tool for determining the permissible scope of patent claims as against a specific structure accused of infringement." *Mannesmann, 793 F.2d at 1284.* Claim amendments and arguments made during the prosecution for a patent may preclude a patentee from recapturing what was foregone during prosecution of the patent application. *Black & Decker Inc. v. Hoover Service Center, 886 F.2d 1285 (Fed. Cir. 1989).* Thus, the doctrine of prosecution history estoppel prevents a patentee "from enforcing its claims against otherwise legally equivalent structures if those structures are excluded by claim limitations added in order to avoid prior art." *Mannesmann, 793 F.2d at 1284.*

The invocation of the doctrine of prosecution history estoppel however, does not automatically preclude the application of the doctrine of equivalents. *Black & Decker, 886 F.2d at 1295.* "That a patent applicant narrows his claim to secure a patent does not [*6] always mean that prosecution history estoppel completely prohibits the patentee from recapturing some of what was originally claimed. The amount of coverage retained depends on the circumstances of each case." *Pennwalt, 833 F.2d at 939.* Both doctrines are equitable in nature, and require courts to engage in a balancing analysis 'guided by equitable and public policy principles underlying the doctrines involved and by the facts of the particular case." *Black & Decker, 886 F.2d at 1295* (quoting *Loctite Corp. v. Ultraseal Ltd., 781 F.2d 861, 871 n.7 (Fed. Cir. 1985).*

C. Plaintiffs' Prosecution History

Defendants argue that the plaintiffs amended their patent claim with regards to the handholds in order to overcome the prior art. Defendants claim that this amendment, which narrowed Plaintiff's patent claim, now estops Plaintiffs from recapturing what they gave up in obtaining their patent.

A review of the prosecution history reveals that Plaintiffs did indeed amend their patent claim with regards to the handholds. In their first patent application, Plaintiffs described the handholds as "a plurality of openings in said slab and disposed adjacent the periphery of said [*7] support surface providing means for gripping the plastic slab to effect sliding movement of

the plastic slab and the patient support thereon." The patent officer rejected Plaintiffs' patent application in its entirety. Referring to a prior patented device, the patent officer said the prior device "teaches a patient support made of plastic with hand holds for gripping when moving the patient to [sic] so modify the structure of A would be obvious to one familiar with the art and not patentable."

The Plaintiffs then amended the description of the handholds to read "said plurality of openings comprising generally rectangular openings having rounded corners and rounded openings for grasping the slab for moving a patient." In explaining this change to the patent officer, the Plaintiffs argued that none of the prior art "discloses the specific shape and location of the claimed rectangular and round openings." (emphasis in original). While the second application was also rejected by the patent officer, the third application, containing the same description of the handholds, was accepted.

Viewing the facts in a light most favorable to the Plaintiffs, the Court agrees with Defendants that [*8] the facts of this specific case require that Plaintiffs be estopped from arguing the doctrine of equivalents. During the prosecution of their patent, Plaintiffs took the position that the rounded handholds coupled with the rectangular handholds were different from a "plurality of openings" because none of the prior art "discloses the specific shape and location of the claimed rectangular and round openings." Now, Plaintiffs are attempting to argue that the plurality of openings on Defendants' accused board are substantially equivalent to the handholds on Plaintiffs' patented board. Once Plaintiffs took the position that their handholds were different in order to overcome the prior art, they cannot now recapture that which they sought to overcome.

D. Balancing of the Equities

The court is mindful that the doctrine of prosecution history estoppel should not be applied hypertechnically, but through a balancing of equities and public policy. Arguments favoring the Plaintiffs are the facts that the handholds may appear substantially equivalent to a layperson and that the Plaintiffs allege that Defendants literally copied Plaintiffs' manufactured board by tracing it from [*9] a catalog. However, the Court also notes that at one time Plaintiffs themselves argued hat the handholds were not equivalent. Moreover, while Defendants may have traced a picture of Plaintiffs' manufactured board, the board that Plaintiffs manufacture is not the board as patented. n1 As patented, Plaintiffs' board is rectangular in shape with rectangular and round handholds. Plaintiffs' manufactured board is octagonal in shape and does not have any round handholds. It is ironic that Plaintiffs argued that the round and rectangular handholds were an improvement over prior art and now do not even manufacture boards with the round handholds. In light of these facts, this Court does not believe that the equities tip in favor of Plaintiffs.

n1 At the summary judgment hearing, Plaintiffs displayed their manufactured board and the Defendants' accused board and asked the Court to make a comparison. The Court noted that while the boards appeared similar, Plaintiffs' board did not appear as it did in the patent drawings.

[*10]

CONCLUSION

After having reviewed the papers, declarations, exhibits, and oral argument, this Court holds that Plaintiffs are estopped from arguing the doctrine of equivalents with regards to the handholds. Since Plaintiff cannot then show that the handholds in Defendants' accused board are substantially equivalent to the handholds in Plaintiffs' patented board, no cause of action for infringement lies. Accordingly, Defendants' motion for summary judgment of non-infringement is GRANTED.

IT IS SO ORDERED.

SUMMARY JUDGMENT - February 26, 1990, Filed

Pursuant to the Order filed February 16, 1989, it is hereby ORDERED, ADJUDGED, and DECREED that Defendants' motion or summary judgment of non-infringement is granted in full and Plaintiffs' first two causes of action are dismissed with prejudice as to all Defendants.

Pursuant to Federal Rule of Civil Procedure 54(b), this Court finds that there is no just reason for delay of an entry of final judgment as to the first two causes of action and hereby expresses the direction of the entry of judgment.

Plaintiffs have represented to the Court that in the event this Court is affirmed on appeal as to its summary judgment order, Plaintiffs will [*11] not pursue the remaining two causes of action. Pursuant to this representation, this Court orders the remaining two causes of action stayed pending the determination of any appeal of the summary judgment order.

IT IS SO ORDERED.

EXHIBIT 8

LEXSEE 1989 us dist lexis 6621

ALLEN-BRADLEY COMPANY, INC., Plaintiff, v. AUTOTECH CORPORATION, MICROFAST CONTROLS CORP., and SHALABH KUMAR, Defendants

No. 86 C 8514

UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF ILLINOIS, EASTERN DIVISION

1989 U.S. Dist. LEXIS 6621

June 1, 1989, Decided

OPINIONBY:
[*1]

HOLDERMAN

OPINION:

MEMORANDUM OPINION AND ORDER

JAMES F. HOLDERMAN, UNITED STATES DISTRICT JUDGE

On September 2, 1988 this court denied defendants' motion for partial summary judgment on counts seven, eight and nine of the complaint. The court determined, inter alia, that a genuine issue of material fact existed as to whether Allen-Bradley had granted an implied license to purchasers of its 1771 rack.

Thereafter on April 19, 1989 this court granted Allen-Bradley's motion for summary judgment on Microfast's counterclaim for infringement of U.S. Patent No. *3,761,882* (the "*'882* patent").

Defendants have now moved for certification of the court's ruling of September 2, 1988 pursuant to *28 U.S.C. § 1292*(b). * Additionally, defendants have requested the court for entry of a final judgment pursuant to Fed. R. Civ. P. 54(b) against Microfast and in favor of Allen-Bradley on Microfast's counterclaim for infringement of the *'882* patent.

> * Actually, defendants would have the court certify the following question for appeal pursuant to *28 U.S.C. § 1292*(b):
>
> Can a defendant which is a supplier of an unpatented circuit board be held liable as a contributory infringer where:
>
> (a) he sells the circuit board to a customer who has purchased from the patent owner the patented circuit board assembly;
>
> (b) unpatented components of the circuit board assembly are capable of non-fringing use; and
>
> (c) such non-infringing use utilizes less than all of the patent claim elements.
>
> See Defendants' Mem. in Support, pp. 6-7. *28 U.S.C. § 1292*(b) nowhere confers upon this court the authority to seek such an advisory opinion. Rather, the statute authorizes the court to certify for immediate appeal an order which involves "a controlling question of law as to which there is substantial ground for difference of opinion," the immediate appeal from which may materially advance the ultimate termination of the litigation. [*2]

Defendants' motions will be granted. Since the court's ruling of September 2, 1988 involves a controlling question of law as to which there is substantial ground for differences of opinion, and since the court believes that resolution of the issue will materially advance the termination of this litigation, the court will certify for immediate appeal its conclusion that a genuine issue of material fact exists as to whether Allen-Bradley granted an implied license to purchasers of its 1771 rack. See Memorandum Opinion and Order, dated September 2, 1988, pp. 2-6.

Furthermore, the court concludes that no just reason exists to delay entry of final judgment with regard to Microfast's counterclaim for infringement of the *'882* patent, and that the additional prerequisites to a Rule 54(b) certification have been satisfied. *Stearns v. Consolidated Management, Inc., 747 F.2d 1105, 1108 (7th Cir. 1984).*

CONCLUSION

For the reasons stated herein, the court's ruling of September 2, 1988 with regard to the existence of a genuine issue of material fact precluding summary judgment on the seventh, eight and ninth counts of the amended complaint is certified for interlocutory appeal pursuant [*3] to *28 U.S.C. § 1292*(b).

Furthermore, final judgment is entered pursuant to Rule 54(b) Fed. R. Civ. P. in favor of Allen-Bradley Company, Inc. and against Microfast Controls Corp. on Microfast's counterclaim for infringement of U.S. Patent No. *3,761,882.*

DATED: June 1, 1989

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

vs.

VYSIS, INC.,

Defendant.

CASE NO. 99-CV- 2668 H (AJB)

Order Denying Motion for Entry of Final Judgment under Rule 54(b)

On June 19, 2001, the Court granted plaintiff Gen-Probe's motion for partial summary judgment that its nucleic acid test for human immunodeficiency virus ("HIV") and hepatitis C virus ("HCV") does not literally infringe the claims of defendant Vysis' U.S. Patent No. 5,750,338 ("the '338 patent"). The Court construed the term "amplifying" as found in the '338 patent as encompassing only non-specific amplification methods.

On June 29, 2001, Vysis filed a Motion for Entry of Final Judgment under Rule 54(b) of the Federal Rules of Civil Procedure. The parties agreed to an expedited briefing schedule on the motion. Gen-Probe filed an Opposition on July 10, 2001 and Vysis filed a Reply on July 13, 2001. The motion is submitted on the papers without oral argument pursuant to Local Rule 7.1(d)(1).

Vysis seeks entry of final judgment against it on Counts I and III of Gen-Probe's Second Amended Complaint pursuant to Rule 54(b) and a stay of all remaining proceedings so that it may pursue an immediate appeal to the Federal Circuit. Count I of the Second Amended Complaint alleges

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that Gen-Probe's HIV and HCV test kits do not infringe the claims of the '338 patent. Count III asks for a declaration of Gen-Probe's rights and obligations under its license with Vysis.

Gen-Probe asserts that the Court's grant of partial summary judgment does not completely resolve Count I because the Court did not address infringement under the doctrine of equivalents. In its Reply, Vysis stipulates that if the Court enters final judgment under Rule 54(b), it will not assert that Gen-Probe's HIV/HCV test infringe under the doctrine of equivalents unless the Court's claim construction is reversed or modified. Vysis also states that should the Federal Circuit affirm the Court's claim construction, it will not later assert that Gen-Probe's HIV/HCV test kits infringe the claims of the '338 patent under the doctrine of equivalents. Nonetheless, the Court declines to direct entry of final judgment as to Count I of the Second Amended Complaint.[1]

Rule 54(b) of the Federal Rules of Civil Procedure gives courts the discretion to direct the entry of a final judgment as to one or more of the claims in a case upon the express determination that there is no just reason for delay. A district court may grant Rule 54(b) certification if it will aid "expeditious decision" of the case. Texaco, Inc. v. Ponsoldt, 939 F.2d 794, 798 (9th Cir. 1991) (quoting Sheehan v. Atlanta Int'l Ins. Co., 812 F.2d 465, 468 (9th Cir. 1987)).[2] However, Rule 54(b) certification is inappropriate when it allows "piecemeal appeals in cases which should be reviewed only as single units." Id. (citations omitted). Partial judgments under Rule 54(b) are reserved for cases where "the costs and risks of multiplying the number of proceedings and of overcrowding the appellate docket" are outweighed by the pressing need for an early and separate judgment. Morrison-Knudsen Co. v. Archer, 655 F.2d 962, 965 (9th Cir. 1981). Partial judgment under Rule 54(b) is proper where there are distinct claims and immediate review of the portions ruled upon will not result in later duplicative proceedings in the trial or appellate court. White Mountain Apache Tribe v. Hodel, 784

[1] The Court also declines to direct entry of final judgment as to Count III of the Second Amended Complaint. In Count III, Gen-Probe seeks a declaration of its rights and obligations under the '338 patent in light of its non-infringement and invalidity challenges. Because the Court has not addressed the invalidity challenges to the '338 patent, Count III is not eligible for Rule 54(b) certification.

[2] The Federal Circuit applies the law of the regional circuit when evaluating a procedural issue, like Rule 54(b) certification, that is not related to patent law. CAE Screenplates Inc. v. Heinrichfielder GmbH & Co., 224 F.3d 1308, 1314-15 (Fed. Cir. 2000).

F.2d 921,923-24 (9th Cir. 1986); Morrison-Knudsen, 655 F.2d at 965. "A similarity of legal or factual issues will weigh heavily against entry of judgment [under Rule 54(b)]." Morrison-Knudsen, 655 F.2d at 965.

The Court's grant of partial summary judgment does not determine whether the '338 patent is valid. Counts Two, Three, Four, Five, and Six of Gen-Probe's Second Amended Complaint each assert that the '338 patent is invalid. Gen-Probe continues to prosecute those causes of action. Vysis argues that these Counts are separable from Count One and that failure to obtain a prompt determination of the scope of the claims may result in an unnecessary delay in determining Gen-Probe's obligation to pay royalties under the '338 patent license agreement with Vysis. Vysis asks for a stay of the proceedings on Gen-Probe's remaining counts until after appeal to the Federal Circuit.

In this case, an interlocutory appeal is not the quickest path to a final and complete resolution of the case. A pre-trial conference has been set in this case for January 14, 2002. At trial, all of the issues in the case can be disposed of and a full factual record can be developed. Entry of final judgment of Count One, when the invalidity issues remain pending, would result in an inefficient use of judicial resources and unnecessary delay in the ultimate resolution of this case.

Consequently, the Court DENIES Vysis Motion for Entry of Final Judgment Under Rule 54(b).

IT IS SO ORDERED.

DATED: 7-18-01

MARILYN L. HUFF, Chief Judge
UNITED STATES DISTRICT COURT

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99-CV-2668H AJB
JUDGE MARILYN L. HUFF

DECLARATION OF DR. JOSEPH O. FALKINHAM IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: May 29, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

I, Joseph O. Falkinham, III, hereby declare as follows:

1. I have personal knowledge of the facts set forth below, and, if called as a witness in this action, I could and would testify competently to the truth thereof.

2. As disclosed in my *Curriculum* Vitae attached hereto as Exhibit 1, I received an A.B. (Bacteriology, 1964) and a Ph.D.(Microbiology, 1969) from the University of California, Berkeley. I served in the United States Air Force Biomedical Sciences Corps directing hospital clinical laboratories from 1969 to 1972 and then accepted appointment as Fellow in Microbiology (postdoctoral fellowship) in the University of Alabama Medical Center (1972-1974). In 1974, I joined the faculty of Virginia Polytechnic Institute and State University. I have been a professor at Virginia Polytechnic Institute and State University for 26 years where, in addition to my teaching duties, I have been engaged extensively in molecular biological research. My research has focused on gene transmission mechanisms in the bacterium *Escherichia coli* (1964-1980) and on the epidemiology, ecology, physiology, and genetics of *Mycobacterium avium* (1975-present). I have published numerous research articles and book chapters, as well as directed numerous graduate student theses and dissertations in this general field.

3. Nucleic acid target capture and amplification are related to my fields of study, and I am familiar with both the non-specific methods of amplification disclosed by U.S. Patent No. 5,750,338 ("the '338 patent") and specific amplification techniques such Gen-Probe's Transcription-Mediated Amplification (TMA) system.

4. I have been retained as an expert witness in this lawsuit. I have reviewed the specification and claims of the '338 patent (Exhibit 8[1]).

SUMMARY OF OPINION

5. It is my opinion that, as of December 21, 1987, a person of ordinary skill in the art would have understood the term "amplifying" as used in the claims of the '338 patent to mean amplifying any nucleic acid sequence present in a sample by use of the non-specific amplification methods described in the '338 specification. Reading the specification, a person of ordinary skill

[1] Unless otherwise specified, all references to Exhibits shall refer to the corresponding exhibit attached to the Notice of Lodgment of Exhibits filed concurrently herewith.

in the art would *not* have understood the term "amplifying" as used in the claims of the '338 patent to mean amplifying by use of sequence-specific amplification methods incorporating specific primers, specific promoters, and/or specific enzymes.

BACKGROUND

6. Several naturally occurring enzymes create copies of nucleic acids in the cells of living organisms (i.e., "*in vivo*") in a process generally called "replication." These replication enzymes include DNA polymerases, RNA polymerases, and transcriptases. Each of these replication enzymes works by binding to a nucleic acid and producing a complementary copy of its sequence. Some of these enzymes (*e.g.*, DNA polymerases) require primers to initiate replication.

7. Each replication enzyme is named for the reaction it catalyzes. For example, a DNA polymerase catalyzes a reaction that produces a DNA polymer strand, while an RNA polymerase catalyzes a reaction that produces an RNA polymer strand.

8. Procedures that amplify DNA in a laboratory are generally performed using replication enzymes and primers, which are short pieces of DNA that bind to a portion of a nucleic acid adjacent to the sequence to be amplified. Amplification takes place when the replication enzymes are able to work in conjunction with the primers to make copies of a nucleic acid sequence.

9. The primer is used to specify the portion of the nucleic acid that will be copied. Primers bind to DNA if there are a sufficient number of complementary base pair matches. The polymerase enzyme then uses the primer as the starting point for its copying action. Generally, in laboratory amplification two primers are used to produce a copy of the sequence that occurs *between* the two points where the primers bind to the target nucleic acid.

10. Like the primers used in the amplification process, the enzymes as well can be specific or non-specific. Specific replication enzymes will only bind to a nucleic acid when the enzyme recognizes a specific sequence of nucleotide bases. However, many of those same enzymes can and have been modified by scientists, or used in particular reaction conditions (e.g., lower than normal salt concentrations), to remove this specific recognition aspect and make them

non-specific so that they can bind to and replicate a variety of different sequences.

11. Primers used in *specific* amplification procedures are selected to bind to a specific, unique sequence in a particular organism's DNA, and no other organism's DNA. Such primers are referred to as "specific" or "sequence-specific" primers. For example, the "Polymerase Chain Reaction" or "PCR" method of amplification, invented by Dr. Kary Mullis and others at Cetus Corporation in 1983, uses sequence-specific primers to amplify a specific nucleic acid sequence that is between the two primers. That specific nucleic acid sequence may be contained within a large collection of sequences, and the method thus defines a specific fragment of DNA to be selectively amplified.

12. While primers are generally designed to be specific to a particular nucleic acid target, it is also possible to produce "random" primers, which are mixtures of primers that contain hundreds and thousands of random nucleotide sequences. These primers are usually collections of short DNA fragments, averaging about 6 nucleotides in length. Short sequences that are complementary to these so-called "random hexamers" occur frequently within virtually all nucleic acids. Thus, they will bind at multiple points along any nucleic acid sequence to serve as initiation sites for replication. The target nucleic acid sequence is replicated as a set of smaller fragments, each beginning with the sequence of its initiating primer. Random hexamer primers have been commercially available since the 1970's. By using "universal" or "random" primers in an amplification process, it is possible to avoid the labor and cost that would be necessary in order to develop specific primers for each target nucleic acid. The trade-off in using random primers is that the amplification process will not be specific for the sequence of interest, and instead will amplify any nucleic acid present in the sample (including sequences that are not of interest).

13. "Specific" primers and enzymes will function together to amplify a target nucleic acid only if the specific sequence of interest bound by the primer(s) and/or recognized by the enzyme is present in the sample. By contrast, non-specific primers and enzymes will amplify *any* sequence present in the sample because some random primers will bind to the sequences in the sample and non-specific replication enzymes will catalyze the reaction without regard to the sequence.

THE MEANING OF CLAIM TERMS IN VIEW OF THE '338 PATENT'S TEACHINGS

14. The '338 patent describes combining target capture with *non-specific* amplification of the captured nucleic acid sequence. By "non-specific amplification," I mean that the primers described in the patent are not pre-selected to bind to specific nucleotide sequences as part of the amplification process. The enzymes described in the patent are also non-specific and will cause replication of any sequence. My opinion about the meaning of the term "amplifying" is based on my understanding of the state of the art at the time the application for the '338 patent was filed and the description of the invention set forth by the inventors in the '338 patent. I discuss the reasons for my opinion below.

Introduction to the Patent Specification

15. In the "Background of the Invention" section, the patent defines the term "amplify" in very broad terms that encompass many different methods of amplification, including many that were already well-known in the art. Throughout the remainder of the specification, however, the inventors teach only non-specific amplification, a subset of the methods known in 1987, because -- the inventors say -- a benefit of their invention is that it *eliminates* the need to design and prepare specific primers and/or the need to use specific enzymes. [The '338 Patent at column 30, lines 30-40.] Thus, the inventors intentionally teach the use of amplification methods that are significantly more limited than the full range of amplification methods known in the art at the time. The inventors' description of their invention narrowed the term "amplify," with respect to the invention, from the general definition initially set forth in the "Background of the Invention."

The Fundamental Teaching Of The '338 Patent

16. The '338 patent presents seven examples of the methods taught by the inventors. In the first three examples, the inventors refer only to methods of target capture, without an amplification step. In the last four examples, the inventors teach combining a target capture step with amplification methods.

17. Between the end of the target capture examples (Examples 1-3) and the first example to add an amplification step (Example 4), the inventors expressly set forth their teachings with respect to amplification methods. Referring to the target capture methods described in

Examples 1 through 3, the inventors stated:

> The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by ***nonspecific*** *replication using standard enzymes* (polymerases and/or transcriptases).

('338 patent, Exh. 8, at col. 30, ll. 14-18, emphasis added.)

18. The inventors then stated *why* they had chosen to combine their target capture methods with non-specific amplification. The inventors stated that the target capture step of their method made specific amplification primers and enzymes unnecessary:

> Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ ***non-specific*** *enzymes or primers...* ***Thus no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of targets.***

(*Id.* at col. 30, ll. 30-40, emphasis added.) A person skilled in the art as of December 1987 would have understood from this description that a primary benefit of this invention was that it used "standard" primers and reagents for all amplification reactions. A person skilled in the art would have understood that, by using the method of the invention, one would not need to design and test specific primers for each particular target organism and/or use other individualized reagents. When the patent says that "no specifically tailored primers are needed ... and the same standard reagents can be used, regardless of targets," one skilled in art would conclude that the invention does not encompass methods of *specific* amplification. In fact, the inventors tell one of ordinary skill in the art that there is no need for specific amplification using their method.

The Drawings and Examples Of The Patent

19. The first pages of the '338 patent provide drawings of various methods encompassed by the invention. The drawings are discussed and described in sections in the sections entitled "Brief Description of the Drawings" and "Detailed Description" ('338 Patent, Exh. 8, at cols. 9-19.) The drawings are also referred to in the "Examples" set forth in the final section of the specification, immediately preceding the claims (Columns 24-32).

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20. The first 3 drawings (Figure 1a to Figure 3) depict target capture methods alone, without amplification. Figures 4, 5 and 6 depict a target capture step followed by an amplification step using only non-specific primers or enzymes. The patent text expressly states that in each of these drawings "the isolated target is *non-specifically* amplified to form a multitude of amplification products." (*Id.* at col. 15, ll. 56-58, emphasis added.)

21. In the "Examples" section of the patent, the inventors set forth seven examples to further describe their invention (*Id.* at col. 24 to 32). As discussed above, the first three examples describe target capture methods, without amplification. After Example 3, the inventors set forth the fundamental teaching of the '338 patent with respect to the use non-specific amplification (discussed in paragraphs 19 and 20 above). Then, the inventors present four examples of amplification methods combined with target capture (Examples 4 - 7). Although these four examples describe different amplification methods, all of those methods describe *non-specific* amplification. Each of these examples is consistent with the earlier teaching of the patent that sequence-specific primers and specific enzymes are not necessary.

22. The Drawings, associated text, and Examples do not describe methods that combine target capture with sequence-specific amplification methods using specific primers or enzymes. The absence of such references is consistent with the patent's core teaching that the burden of specific amplification methods can be avoided when the inventor's methods are used.

Figure 4 and Example 4

23. Figure 4 and Example 4 of the '338 patent describe only a form of non-specific amplification, namely, non-specific transcription.

24. In describing Figure 4, the patent states that the amplification reaction uses "core RNA polymerase" to produce to produce a complementary RNA. (Col. 15, ll. 59-61; see also Fig. 4, Step 3). Core RNA polymerase lacks an accessory protein (the sigma protein) that endows the core enzyme with the ability to bind to certain nucleotide sequences and initiate RNA synthesis (Example 4, column 30, lines 59-66). The core RNA polymerase, lacking sigma protein, binds anywhere on a DNA, thus producing a variety of complementary sequences (Figure 4, step 3, and Example 4 (Col. 31, lines 5-16)). Thus, core RNA polymerase amplifies non-specifically by

transcribing[2] *any* sequence with which it comes into contact. Example 4 further states that other "RNA polymerases *that lack transcriptional specificity*..." can be used in place of the particular polymerase suggested by the inventors (Col. 30, line 66 to col. 31, line 1).

25. Figure 4 and Example 4 describe only non-specific amplification. Figure 4 and Example 4 do not describe the use of sequence-specific primers or enzymes in the amplification step. The method described by the inventors in Example 4 is consistent with their earlier teaching that no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of targets.

Figure 5 and Example 5

26. Figure 5 and Example 5 describe a form of non-specific amplification in which the isolated target DNA is non-specifically replicated and then non-specifically transcribed:

> In this example, both *non-specific* replication of target DNA and transcription of that DNA are used to amplify capture target DNA.... Because the primers are *random*, some will, simple (sic) as a matter of statistics, bind to and cause replication of sample sequences, no matter what those sequences are. . . .

('338 Patent, Exh. 8, at col. 31, l. 24-54, emphasis added.)

27. In Figure 5, the inventors describe a "two enzyme amplification system" that uses, first, in step 3(a), a DNA polymerase with random hexamer primers to make DNA strands, and second, in step 3(b), core RNA polymerase to form additional RNA complements of the DNA (Col. 16, ll. 10-16; Example 5, col. 31, lines 25-53). As previously set forth, core RNA polymerase amplifies *non-specifically.*

28. Further, because of the limited number of primers of the same sequence in the mixture of random hexamers, there would be little accumulation of specific sequences. The primers become part of the amplified product and are thus consumed.

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[2] "Transcription" is a process of nucleic acid synthesis in which an RNA polymerase makes a single-stranded RNA copy of a DNA strand. Transcription does not require primers. In non-specific transcription, the RNA polymerase initiates synthesis randomly at multiple points along the DNA. Specific transcription occurs when the RNA polymerase with sigma protein recognizes and binds to a specific sequence in the DNA called a "promoter." The RNA is then synthesized beginning at that point.

29. The "hexamer primers" and "random oligohexamer primers" described in Figure 5, step 3a, and Example 5 (col. 31, lines 31-32) are commercially available pieces of DNA six bases long, that are a collection of random nucleotide sequences (see col. 31, lines 32-33). The hexamer primers and DNA polymerase depicted in Figure 5, step 3a, would indiscriminately replicate any nucleic acid sequences present in the reaction mixture, which is explicitly stated in Example 5 ("*non-specific* replication of target DNA." (Col. 31, ll. 24-25, emphasis added.)) Thus, a family of different sequences would be produced as a result of the non-specific amplification. Further, because mixtures of random hexamers will vary, the products of non-specific amplification would differ from individual experiment to experiment.

30. In the second enzyme step described in Figure 5, step 3b, and in Example 5, non-specific RNA polymerase is added to non-specifically produce many RNA copies from the DNA.

31. Thus Figure 5 and Example 5 describe only non-specific amplification. The inventors described and illustrated a method that is consistent with the teaching of the patent that no specifically tailored primers are needed for each test, and that standard reagents can be used, regardless of target nucleic acid.

Figure 6 and Example 6

32. Figure 6 and Example 6 describe only non-specific amplification of a "captured" nucleic acid, using DNA polymerase and "non-specific" or "random hexamer primers" to bring about non-specific double-stranded DNA synthesis (Figure 6, Step 3a; col. 16, lines 17-23; Example 6, col. 31, lines 63-64).

33. The amplification process described in Example 6 and illustrated in Figure 6 is a cycling method similar to the cycles of synthesis used in the PCR method, but the method described in the '338 patent does not use sequence-specific primers. Instead, the method taught by the inventors in the '338 patent describes the use of a target capture step to isolate the target nucleic acid from other nucleic acids, followed by multiple cycles of DNA synthesis, each initiated by using random hexamer (e.g., non-specific) primers. There would be no accumulation of unique sequences, because of the consumption of primers during non-specific amplification.

34. Example 6 states that the amplification step described therein (and depicted in Figure 6) uses DNA polymerase and "*random* hexamer oligonucleotides to bring about *non-specific* double-stranded DNA synthesis" ('338 Patent, Exh. 8, at col. 31, ll. 63-64, emphasis added).

35. Thus Figure 6 and Example 6 describe only non-specific amplification. The method described by the inventors in Example 6 is consistent with their teaching that no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of the target sequence.

Example 7

36. In Example 7, the inventors describe another method of non-specific amplification. (There is no drawing in the patent that depicts the method of Example 7.)

37. In Example 7, the inventors describe a *non-specific* amplification method that uses an RNA polymerase, Qß replicase:

> In this example, rRNA and RNA transcribed from target DNA is purified using a capture probe, described above. The hybrid duplex is then denatured and single stranded nucleic acids are then replicated *non-specifically* using Qß replicase...

('338 Patent, Exh. 8, at col. 32, l. 10-19, emphasis added.)

38. Thus Example 7, like Examples 4, 5 and 6, also discloses only non-specific amplification of a captured nucleic acid. This method is also consistent with the inventors' teaching that the methods of their invention do not require specifically designed or predetermined primers and that the same reagents and replicase can be used for each test, regardless of the target.

Procedures

39. The '338 patent describes certain procedures to be used in connection with the invention (columns 19-24).

40. In the "Procedures" section, the inventors did not prescribe any procedures for designing, making, or using sequence-specific primers or enzymes, nor any procedures for combining target capture with methods of specific amplification. This omission is consistent with the teaching of the patent that specifically tailored primers are not needed for any test, and the

same standard reagents can be used.

The Understanding of A Person of Ordinary Skill in the Art at the Time of Filing

41. I understand that a term in a patent claim will be given the meaning that would have been understood, based on the description provided by the inventors in the patent, by one of ordinary skill in the art. I further understand that the meaning is determined as of the date on which the first patent application was filed for the claimed invention. I have been informed that the applicable date in this case is December 21, 1987.

42. A person of ordinary skill in the art in December 1987, reading the '338 patent specification, would understand the term "amplifying" in the claims to mean using non-specific amplification methods (such as those described and illustrated in the patent).

43. In the '339 patent, the inventors explicitly teach that the benefit of their invention is that it allows the use of non-specific amplification. The inventors apparently believed that the specificity of the target capture step of their method permitted scientists to avoid the need for specific amplification:

> The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by ***nonspecific*** *replication using standard enzymes* (polymerases and/or transcriptases).

('338 patent, Exh. 8, at col. 30, ll. 14-18, emphasis added.)

> Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ ***non-specific*** *enzymes or primers...* ***Thus no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of targets.***

(*Id.* at col. 30, ll. 30-40, emphasis added.)

44. This express teaching of the patent is reinforced by the fact that the only amplification methods that the inventors chose to describe and illustrate with Examples and Drawings are non-specific amplification methods.

45. Further reinforcing my conclusion is the fact that PCR, the most commonly used sequence-specific amplification method at the filing date, is not included, described or referenced in the specification. Moreover, the specification does not contain a reference to any other

sequence-specific amplification method.

46. If the inventors had intended to suggest and claim the combination of target capture with sequence-specific amplification methods such as PCR, it would have been easy for them to do so. The PCR method was first described at a scientific meeting in the summer of 1985 and was published in December 20, 1985. Within the scientific community, PCR was immediately recognized as a significant improvement over earlier methods of making copies of nucleic acids, and knowledge of the method was widespread.

47. Although the application leading to the '338 patent was filed two years after PCR was publicly disclosed, the patent does not describe or teach a method that combines target capture with amplification methods using specific primers, such as PCR.

48. Although the '338 inventors could have included an example in the patent that combined target capture and sequence-specific amplification (such as PCR), the inventors instead described a method to *avoid* using sequence-specific primers. That is, the inventors suggested their invention as an *alternative* to specific primer methods such as PCR.

49. In all of their drawings, descriptions, and examples included in the '338 patent, the inventors clearly taught that by adding the specificity of a target capture step, scientists could avoid the need to use specific primers and enzymes in the amplification step of a nucleic acid assay.

50. I understand that the patent statute requires that the patent set forth enough details to enable a person skilled in the art to make and use the invention, as it is claimed, without requiring more than routine experimentation. It is unclear to me how the '338 patent enables a person of ordinary skill in the art as of December 1987 to use methods that combined target capture and sequence-specific amplification techniques, when no such methods were described in the patent.

51. I also have been informed that the patent statute requires that the "written description" of the invention set forth in the specification patent must demonstrate that the inventor(s) had actually invented the invention, *as it is claimed*, when the patent application was filed. The '338 patent does not show that the inventors invented any methods that combined target

capture with sequence-specific amplification, and the patent in fact tells those skilled in the art that specific amplification is not necessary when the invention of the patent is employed. Specific amplification cannot, therefore, be a part of the invention.

SUMMARY

52. A person of ordinary skill in the art, reading the '338 patent, would understand the term "amplifying" as used in the claims to mean amplifying with the methods of non-specific amplification described in the patent. Moreover, upon reading the '338 patent, a person of ordinary skill in the art would not have understood the term "amplifying" as used in the claims to mean amplifying by using sequence-specific primers, and/or specific enzymes in methods of sequence-specific amplification.

I hereby declare under penalty of perjury under the laws of the United States of America that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. As discovery in this case is now just beginning, I reserve the right to change my opinion. This declaration was executed by me on this 26th day of April, 2001 at Blacksburg, Virginia.

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Mayer, B.K. and J.O. Falkinham, III. 1986. Superoxide dismutase activity of *Mycobacterium avium, M. intracellulare* and *M. scrofulaceum*. Infect. Immun. *53*:631-635.

Pittinger, C.A., A.L. Buikema, Jr. and J.O. Falkinham, III. 1987. *In situ* variations in oyster mutagenicity and tissue concentrations of polycyclic aromatic hydrocarbons. Environ. Tox. Chem. *6*:51-60.

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Erardi, F.X., M.L. Failla and J.O. Falkinham, III. 1987. Plasmid-encoded copper resistance and precipitation by *Mycobacterium scrofulaceum*. Appl. Environ. Microbiol. *53*:1951-1954.

Erardi, F.X., M.L. Failla and J.O. Falkinham, III. 1989. Accumulation and transport of cadmium by tolerant and susceptible *Mycobacterium scrofulaceum*. Antimicrob. Agents Chemother. *33*:350-355.

George, K.L. and J.O. Falkinham, III. 1989. Identification of cytoplasmic membrane protein antigens of *Mycobacterium avium, M. intracellulare,* and *M. scrofulaceum*. Canad. J. Microb. *35*:529-534.

Pethel, M.L. and J.O. Falkinham, III. 1989. Plasmid-influenced changes in *Mycobacterium avium* catalase activity. Infect. Immun. *57*:1714-1718.

Falkinham, J.O., III, K.L. George and B.C. Parker. 1989. Epidemiology of infection by nontuberculous mycobacteria. VIII. Absence of mycobacteria in chicken litter. Am. Rev. Respir. Dis. *139*:1347-1349.

Gross, W.B., J.O. Falkinham, III and J.B. Payeur. 1989. Effect of social environment and antibody responsiveness on *Mycobacterium avium* infection in chickens. Avian Diseases *33*:411-415.

Stormer, R.S. and J.O. Falkinham, III. 1989. Differences in antimicrobial susceptibility of colonial variants of *Mycobacterium avium*. J. Clin. Microbiol. *27*:2459-2465.

Carlisle, G.C. and J.O. Falkinham, III. 1989. Enzyme activities and antibiotic susceptibility of colonial variants of *Bacillus subtilis* and *Bacillus licheniformis*. Appl. Environ. Microbiol. *55*:3026-3028.

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Jucker, M.T. and J.O. Falkinham, III. 1990. Epidemiology of infection by nontuberculous mycobacteria. IX. Evidence for two DNA homology groups among small plasmids in *M. avium, M. intracellulare*, and *M. scrofulaceum*. Am. Rev. Respir. Dis. *142*:858-862.

Via, L.E. and J.O. Falkinham, III. 1991. Isolation of restriction fragments from large plasmids recovered from bacteria with multiple plasmids. BioTechniques *11*:442-443.

Taber, R.A., M.A. Thielen, J.O. Falkinham, III, and R.H. Smith. 1991. *Mycobacterium scrofulaceum*: a bacterial contaminant in plant tissue culture. Plant Sci. *78*:231-236.

Kirschner, R.A., Jr., B.C. Parker, and J.O. Falkinham, III. 1992. Epidemiology of infection by nontuberculous mycobacteria. X. *Mycobacterium avium, M. intracellulare*, and *M. scrofulaceum* in acid, brown-water swamps of the southeastern United States and their association with environmental variables. Am. Rev. Respir. Dis. *145*:271-275.

Morrissey, A.B., T.O. Aisu, J.O. Falkinham, III, P.P. Eriki, J.J. Ellner, and T.M. Daniel. 1992. Absence of *Mycobacterium avium* complex in patients with AIDS in Uganda. J. AIDS 5:477-478.

Arbeit, R.D., A. Slutksy, T.W. Barber, J.N. Maslow, S. Niemczyk, J.O. Falkinham, III, G.T. O'Connor, and C.F. von Reyn. 1993. Genetic diversity among strains of *Mycobacterium avium* causing monoclonal and polyclonal bacteremia in patients with AIDS. J. Infect. Dis. *167*:1384-1390.

von Reyn, C.F., R.D. Waddell, T. Eaton, R.D. Arbeit, J.N. Maslow, T.W. Barber, R.J. Brindle, C.F. Gilks, J. Lumio, J. Lähdevirta, A. Ranki, D. Dawson, and J.O. Falkinham, III. 1993. Isolation of *Mycobacterium avium* complex from water in the United States, Finland, Zaire, and Kenya. J. Clin. Microbiol. *31*:3227-3230.

Ijzerman, M.M., J.O. Falkinham, III, and C. Hagedorn. 1993. A liquid, colorimetric presence-absence coliphage detection method. J. Virol. Methods *45*:229-234.

Ijzerman, M.M., J.O. Falkinham, III, R.B. Reneau, Jr., and C. Hagedorn. 1994. Field evaluation of two colorimetric coliphage detection methods. Appl. Environ. Microbiol. *60*:826-830.

von Reyn, C.F., J.N. Maslow, T.W. Barber, J.O. Falkinham, III, and R.D. Arbeit. 1994. Persistent colonisation of potable water as a source of *Mycobacterium avium* infection in AIDS. Lancet *343*:1137-1141.

Reddy, V.M., K. Parikh, J. Luna-Herrera, J.O. Falkinham, III, S. Brown, and P.R.J. Gangadharam. 1994. Comparison of virulence of *Mycobacterium avium* complex (MAC) strains isolated from AIDS and non-AIDS patients. Microbial Pathogen. *16*:121-130.

Falkinham, J.O., III. 1994. Epidemiology of *Mycobacterium avium* infection in the pre- and post-HIV era. Res. Microbiol. *145*:169-172.

Via, L.E. and J.O. Falkinham, III. 1995. Comparison of methods for isolation of *Mycobacterium avium* complex DNA for use in PCR and RAPD fingerprinting. J. Microbiol. Meth. *21*:151-161.

Eaton, T., J.O. Falkinham, T.O. Aisu, and T.M. Daniel. 1995. Isolation and characteristics of *Mycobacterium avium* complex from water and soil samples in Uganda. Tubercle Lung Dis. *76*:570-574.

Eaton, T., J.O. Falkinham, III, and C.F. von Reyn. 1995. Recovery of *Mycobacterium avium* from cigarettes. J. Clin. Microbiol. *33*:2757-2758.

Warek, U. and J.O. Falkinham, III. 1996. Action of clofazimine on the *Mycobacterium avium* complex. Res. Microbiol. *147*:43-48.

Rastogi, N. and J.O. Falkinham, III. 1996. Solving the dilemma of antimycobacterial chemotherapy. Res. Microbiol. *147*:7-10.

von Reyn, C.F., R.D. Arbeit, A.N.A. Tosteson, M.A. Ristola, T.W. Barber, R. Waddell, C.H. Sox, R.J. Brindle, C.F. Gilks, J. Edwards, J.O. Falkinham, III, G.T. O'Connor. 1996. The international epidemiology of disseminated *Mycobacterium avium* complex infection in AIDS. AIDS 10:1025-1032.

Ristola, M.A., C.F. von Reyn, R.D. Arbeit, H. Soini, J. Lumio, A. Ranki, S. Bühler, R. Waddell, A.N.A. Tosteson, J.O. Falkinham, III, and C.H. Sox. 1999. High rates of disseminated infection due to non-tuberculous mycobacteria among AIDS patients in Finland. J. Infection 39:61-67.

Kirschner, R.A., B.C. Parker, and J.O. Falkinham, III. 1999. Humic and fulvic acids stimulate the growth of *Mycobacterium avium*. FEMS Microbiol. Ecol. 30:327-332.

Taylor, R.H., J.O. Falkinham, III, C.D. Norton, and M.W. LeChevallier. 2000. Chlorine-, Chloramine-, Chlorine Dioxide- and Ozone-susceptibility of *Mycobacterium avium*. Appl. Environ. Microbiol. 66:1702-1705.

Cain, C.C., A.T. Henry, R.H. Waldo, III, L.J. Casida, Jr., and J.O. Falkinham, III. 2000. Identification and characteristics of a novel *Burkholderia* strain with broad-spectrum antimicrobial activity. Appl. Environ. Microbiol. 66:4139-4141.

Stanek, J.E. and J.O. Falkinham, III. 2001. Rapid coliphage detection assay. J. Virol. Meth. 91:93-98.

Falkinham, J.O., III, C.D. Norton, and M.W. LeChevallier. 2001. Factors influencing numbers of *Mycobacterium avium, Mycobacterium intracellulare*, and other mycobacteria in drinking water distribution systems. Appl. Environ. Microbiol. 67:1225-1231.

Cowan, H. E. and J. O. Falkinham, III. In Press. A luciferase-based method for assessing chlorine-susceptibility of *Mycobacterium avium*. J. Microbiol. Meth.

RESEARCH GRANTS AND FINANCIAL SUPPORT

1999-2002 Physiological Ecology of Mycobacteria
Applied Microbiology and Genetics, $ 100,000

1998-2001 Genetic Studies of *Burkholderia casidae* strain 2.2 N
Dominion Biosciences, Inc., $ 101,000

1997-1999 PCR Detection of Mycobacteriosis in Aquaculture of Fish
NOAA, Sea Grant Program, $ 120,000.

1996-1999 Occurrence and Control of *Mycobacterium avium* Complex,
American Water Works Association Research Foundation,
$ 250,000.

1996-1998 Predator Fungicide Development,
Dominion Biosciences, Inc., $ 175,000.

1993-1995 Commercial Development of a Rapid Coliphage Assay,
Virginia Center for Innovative Technology, $ 128,515.

1991-1994 Disseminated *Mycobacterium avium* in AIDS,
National Institute of Allergy and Infectious Disease,
$ 267,550.

1991-1994 Clofazimine Action in Mycobacteria,
Heiser Program for Research in Leprosy, $ 18,315.

1989-1990 Mechanism of Clofazimine Resistance in *Mycobacterium avium*,
The Potts Foundation, $ 5,300.

1987-1990 Epidemiology of Infection by Atypical Mycobacteria,
National Institute of Allergy and Infectious Diseases,
$ 338,208.

1986-1987 Comparison of Mitochondrial DNA from Dairy and Beef Cattle Breeds,
Biomedical Research Support Grant, $ 2,100.

1983-1986 Epidemiology of Infection by Atypical Mycobacteria,
National Institute of Allergy and Infectious Disease,
$ 503,410.

1983-1984 Proof of Relatedness of Mercury- and Cadmium-resistant Human and
Environmental Isolates of *Mycobacterium avium*, *M. intracellulare*,
and *M. scrofulaceum*. Biomedical Research Support Grant, $ 2,000.

1982-1983 Improvement in Silage Fermentation Through Genetic Engineering of
Lactobacilli, George A. Jeffreys and Co., Inc. $ 1,800.

1980-1982 Analysis of the *lon*-locus of *Escherichia coli* K-12,
National Institute of Allergy and Infectious Disease,
$ 28,733.

1979-1982 Epidemiology of Infection by Atypical Mycobacteria,
National Institute of Allergy and Infectious Diseases,
$ 350,098.

1977-1980 Membrane Involvement in Bacterial Conjugation,
National Institute of Allergy and Infectious Diseases,
$ 51,101.

1977-1979 Epidemiology of Infection by Atypical Mycobacteria,
National Institute of Allergy and Infectious Diseases,
$ 120,323.

1977-1978 Occurrence, Distribution, and Detection of Water-borne Bacterial
Pathogens, Virginia Office of Water Resources Research, $ 15,907.

THESES AND DISSERTATIONS DIRECTED

Taylor, R.T. (M.S., Microbiology, 1998), "Chlorine, Chloramine, Chlorine Dioxide, and Ozone susceptibility of *Mycobacterium avium.*"

Cowen, H.E. (M.S. Microbiology, 1998), "Rapid, Quantitative Assessment of *Mycobacterium avium* Susceptibility to Chlorine Based on the Firefly Luciferase Reporter Gene."

Jensen, D.M. (Ph.D., Microbiology, 1997), "Genetic Basis for Macrolide Resistance in *Mycobacterium avium*".

Stanek, J.E. (M.S., Microbiology, 1997), "Development of a Rapid Coliphage Detection Assay".

Eaton, T. (M.S., Microbiology, 1993), "Epidemiology of *Mycobacterium avium* complex infecting AIDS patients".

Via, L.E. (Ph.D., Microbiology, 1993), "Insertion sequence IS1141: Discovery, characterization and association with *Mycobacterium avium* colonial variation".

Jucker, M.T. (Ph.D., Microbiology, 1991), "Identification and characteristics of plasmid homology groups of *Mycobacterium avium, M. intracellulare,* and *M. scrofulaceum*".

Carlisle, G.C. (M.S. Microbiology, 1991), "Isolation and characterization of the major cytoplasmic membrane protein of *Mycobacterium avium*".

Warek, U. (M.S., Microbiology, 1990), "Mechanism of action of clofazimine in *Mycobacterium avium* and *Mycobacterium intracellulare*".

Stormer, R.S. (M.S. Microbiology, 1989), "Differences in antimicrobial susceptibility of pigmented and unpigmented colonial variants of *Mycobacterium avium*".

Pethel, M.L. (M.S. Microbiology, 1988), "Plasmid-influenced changes in *Mycobacterium avium* catalase".

Erardi, F.X. (M.S. Microbiology, 1986), "Characterization of cadmium susceptibility in *Mycobacterium avium, M. intracellulare* and *M. scrofulaceum.*"

Mayer, B.K. (M.S. Microbiology, 1985), "Investigation of catalase and superoxide dismutase from *Mycobacterium avium, M. intracellulare,* and *M. scrofulaceum*".

Fry, K.W. (M.S. Microbiology, 1984), "Comparison of environmental and clinical strains of *Mycobacterium avium, M. intracellulare* and *M. scrofulaceum*".

Meissner, P.S. (Ph.D. Genetics, 1984), "Plasmids of *Mycobacterium avium, M. intracellulare* and *M. scrofulaceum*: isolation, use as epidemiological markers and role in heavy metal-resistance".

Cosby, W.M. (M.S. Microbiology, 1984), "Genetic engineering lactobacilli for improved alfalfa ensiling and citrate resistance".

Smith, R.T. (Ph.D. Microbiology, 1983), "Effect of temperature-induced membrane lipid phase transitions in recipient cells on conjugation in *Escherichia coli* K-12".

Brooks, R.W. (M.S. Microbiology, 1983), "Soil as a possible origin of organisms of the *Mycobacterium avium, M. intracellulare* and *M. scrofulaceum* (MAIS) complex in the southeastern United States".

Torres-Cabassa, A.S. (Ph.D. Genetics, 1982), "Genetic analysis and phenotypic characterization of Lon⁻ mutants of *Escherichia coli* K-12".

Winfield, S.L. (M.S. Microbiology, 1979), "Genetic duplication in *Salmonella typhimurium*".

Ferguson, K.P. (M.S. Microbiology, 1978), "Identification of a mutation affecting plasmid establishment in *Escherichia coli* K-12".

Fiore, J.D. (M.S. Microbiology, 1978), "Studies of the utility of lectin-induced agglutination and bacteriophage adsorption in determining bacterial lipopolysaccharide composition".

TEACHING

Genetics - Sophomore introductory genetics course.

Genetics Laboratory - Sophomore laboratory course in genetic techniques.

Microbiology - Sophomore introduction to all aspects of microorganisms.

Microbial Genetics - A senior and graduate level course on the genetics of eukaryotic and prokaryotic microorganisms and their viruses.

Molecular Biology - A junior and senior level course on eukaryotic and prokaryotic molecular biology and recombinant DNA technology.

Topics in Microbial Genetics - Graduate, rotating topics course in microbial genetics.

Molecular Biology Laboratory - A senior and graduate level laboratory course in molecular biological techniques.

Humanities and the Biological Sciences - Course in the Humanities, Science, and Technology Program on issues surrounding genetic engineering.

ADMINISTRATIVE AND DEPARTMENTAL SERVICE

University

Promotion and Tenure Committee, 1997-1999
Vice President, Faculty Senate, 1991-1992
Secretary/Treasurer, Faculty Senate, 1990-1991
Senator, Faculty Senate, 1989-1993
Chair, Faculty Senate Committee on Reconciliation, 1991-1994
Member, Laboratory & Hazardous Material Committee, 1995-present
Chair, Commission on University Support, 1992-1993
Chair, Commission on Faculty Affairs, 1991-1992
Chair, Interdepartment Genetics Program, 1981-1982
University Pre-Medical/Dental Advising Committee, 1975-1981

College

Personnel Committee, College of Arts and Sciences, 1994-1996
Secretary, College of Arts and Sciences Faculty Senate, 1989-1990
Liberal Arts and Sciences Major Advisory Committee, 1980-1988
Humanities, Science and Technology Faculty, 1976-1990

Department

Graduate Advisor, 1991-1996
Chair, Molecular Cell Biologist Search Committee, 1992-1993
Chair, Microbiologist Search Committee, 1994-1995
Member, Microbiologist Search Committee, 1995-1996
Member, Curriculum Committee, 1990-1993
Member, Graduate Selection Committee 1988-1989
Member, Graduate Diagnostic and Qualifying Examination Committee, 1984-1988
Member, Research Committee, 1974-1976
Member, Biology Department Head Evaluation Committee, 1975
Member, Safety Committee, 1975-1990
Member, Self Study Committee, 1975-1976
Chair, Undergraduate Awards Committee, 1979-1980

PROFESSIONAL SERVICE

American Society for Microbiology
Nominee, Mycobacteriology Division Chair, 1992
Chair, Mycobacteriology Division Nominations Committee, 1990
Member, Mycobacteriology Division Program Committee, 1989
Member, Mycobacteriology Division Nominations Committee, 1988

PUBLIC AND PERSONAL SERVICE

Episcopal Diocese of Southwestern Virginia
Member, Standing Committee, 1990-1993
Member, Executive Committee, 1986-1989
Chair, Grace House Mission Committee, 1979-1992
Blacksburg Chamber of Commerce
Vice President, Government Affairs, 1986-1989
Executive Board, 1984-1989
Faculty Advisor
Gamma Beta Phi (Scholarship, Service), 1988-1996
Sigma Alpha Epsilon (Fraternity), 1983-present

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99-CV-2668H AJB
JUDGE MARILYN L. HUFF

DECLARATION OF DR. MATTHEW LONGIARU IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: May 29, 2001
Time: 10:30 a.m.
Dept: Courtroom 1

I, Mat Longiaru, declare as follows:

1. I am employed by plaintiff Gen-Probe Incorporated as Vice President, Diagnostic Development. I have been employed by Gen-Probe since February 1991.

2. As disclosed in my *Curriculum* Vitae attached hereto as Exhibit 1, I received a B.S.

(Biology) from the City College of New York in 1975, an M.S. (Microbiology) from Long Island University in 1977, and a Ph.D. (Microbiology and Immunology) from Albert Einstein College of Medicine in 1981.

3. As a result of my education and experience, I am familiar with methods of nucleic acid target capture and amplification. I understand methods of non-specific amplification as disclosed in the examples by U.S. Patent No. 5,750,338 ("the '338 patent") and methods of specific amplification, such as Gen-Probe's patented Transcription-Mediated Amplification (TMA) process.

4. I have read the Scientific Background section of the accompanying memorandum in support of summary judgment. The Scientific Background section presents an accurate summary of information about the nucleic acid methods discussed therein.

TMA Uses Sequence-Specific Primers to Achieve Specific Amplification

5. Gen-Probe's HIV-1/HCV Assay ("the Blood Screening Assay") detects small quantities of HIV (human immunodeficiency virus) and HCV (hepatitis C virus) in blood by capturing the viral nucleic acids (i.e., the target nucleic acids) from a sample of blood and amplifying them. The Blood Screening Assay incorporates Gen-Probe's patented TMA technology to *specifically* amplify the captured viral nucleic acids

6. Gen-Probe's Blood Screening Assay achieves specific amplification in part by employing sequence-specific primers, which are designed and made to bind only to specific sequences of interest in the target HIV and HCV nucleic acids. The TMA process will only amplify nucleic acid captured from a sample if the primers find and bind to their respective specific target sequences.

7. One of the two enzymes used in Gen-Probe's Blood Screening Assay is reverse transcriptase ("RT"). Reverse transcriptase is a DNA polymerase that produces a complementary DNA strand copy of a single-stranded RNA or DNA that has a bound primer. In TMA, reverse transcriptase produces complementary DNA from the target nucleic acids (or their complementary strands) only if the sequence-specific primers (described in paragraph 6) first bind to a single strand of RNA or DNA. That is, if the target organism is not present in the sample, the primers

will be unable to bind to the captured sequence and the reverse transcriptase will not initiate synthesis. Therefore the action of the RT enzyme is dependent on the specific primers.

TMA Also Uses Specific Promoters and Enzymes to Achieve Specific Amplification

8. In addition to its target-specific sequence, some of the TMA primers used in the Blood Screening Assay contain a "promoter" sequence that allows a specific enzyme, an RNA "T7 polymerase," to *specifically* bind to and produce RNA copies of the target nucleic acids as part of the TMA amplification process.

9. A functional "T7 promoter" is formed in the course of the TMA process if, and only if, the primer finds and binds to its complementary target sequence in the captured target molecule so that the target sequence is copied by reverse transcriptase. If the T7 promoter *is* formed as a result of primer binding to the target sequence, then the T7 RNA polymerase used in Gen-Probe's Blood Screening Assay will amplify the sequence attached to the T7 promoter sequence. The T7 RNA polymerase does not amplify other sequences present in the sample because they are not attached to a T7 promoter sequence. Thus, in the Blood Screening Assay, the T7 polymerase enzyme *specifically* recognizes the T7 promoter sequence, which has been *specifically* attached to the target sequence by the binding of *specific* primers, and the T7 polymerase *specifically* amplifies only that sequence.

10. In the TMA process, one of the primers *specifically* binds to the newly transcribed RNA and reverse transcriptase makes a new complementary DNA copy of that RNA. The process repeats in a cyclic fashion, resulting in exponential amplification only of the particular target sequence of interest as a consequence of the use of sequence-specific primers, specific promoter sequences, and specific RNA polymerase enzymes. This process safeguards against amplification of non-target sequences and thus protects against false positive results.

11. The TMA method used in the Blood Screening Assay differs substantially from the non-specific amplification methods disclosed in the '338 patent. All of the methods described in the examples of the '338 patent *non-specifically* amplify any nucleic acids captured from the sample, whether those nucleic acids are the intended target or are some other nucleic acid present in the sample after target capture. Unlike the non-specific amplification methods described in the

'338 patent, the TMA process will not amplify non-target sequences that might be retained on the solid support after the target capture step. The sequence-specific primers, specific promoters, and specific RNA polymerase enzymes used in TMA are designed to only amplify their intended target nucleic acids, even if other sequences are present.

I hereby declare under penalty of perjury under the laws of the United States of America that all statements made herein of my own knowledge true and that all statements made on information and belief are believed to be true. This declaration was executed by me on this 24 day of April, 2001 at San Diego, California.

Matthew Longiaru

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CURRICULUM VITAE

NAME:	Mathew Longiaru, Ph.D
ADDRESS:	2772 Galicia Way Carlsbad, CA 92009
PHONE:	(619) 410-8801 (Work) (760) 942-2260 (Home) (619) 410-8871 (Fax) matl@gen-probe.com (email)
BIRTHDATE:	December 21, 1951
BIRTHPLACE:	New York City, New York
MARITAL STATUS:	Married, two children
EDUCATION:	City College of New York, C.U.N.Y. New York, New York Bachelor of Science, 1975
	Long Island University Brooklyn, New York Master of Science, 1977
	Albert Einstein College of Medicine Sue Golding Graduate Division Bronx, New York Doctor of Philosophy, 1981

RESEARCH AND DEVELOPMENT EXPERIENCE:

February 2000 to Present
Vice-President
Diagnostic Development
Gen-Probe Incorporated

May 1996 to January 2000
Senior Director
Research and Development
Gen-Probe Incorporated

October 1995 to April 1996
Director of Research
Gen-Probe Incorporated

February 1991 to September 1995
Director, Advanced Technology Programs
Gen-Probe Incorporated
San Diego, California

October 1987 to February 1991
Research Group Leader
Molecular Biology/DNA Probes
Roche Diagnostic Systems
Nutley, New Jersey

June 1984 to September 1987
Senior Research Scientist
Diagnostic Research, Hoffmann-LaRoche, Inc.
Nutley, New Jersey

Molecular Cloning and Expression of Bioluminescent
Proteins and Human Retroviral Genes
Development of Diagnostic DNA Probe Assays

January 1984 to May 1984
Research Associate
Department of Molecular Genetics
Hoffmann-LaRoche, Inc.

1981 to 1983
Post Doctoral Fellow
Department of Cell Biology
Roche Institute of Molecular Biology
Nutley, New Jersey
Post Doctoral Advisor - Dr. Anne Skalka

The Role of Retroviral Reverse Transcriptase
in Integrative Recombination

1977 to 1981
Pre Doctoral Fellow
Department of Microbiology and Immunology
Albert Einstein College of Medicine
Bronx, New York

Graduate Thesis Advisor - Dr. Marshall Horwitz
Doctoral Thesis - The DNA Polymerases
Involved in Adeno Virus DNA Replication
1976 to 1977
NSF Grant Research Associate
Long Island University
Brooklyn, New York
Antimicrobial agents directed against
Staphylococcus aureus

HONORS AND FELLOWSHIPS:

Graduate Assistant, Long Island University, 1975 to 1976

National Science Foundation
Grant Research Assistant, 1976 to 1977

Phi Sigma Award, Long Island University, 1977

National Institute of Health
Graduate Traineeship, 1977 to 1981

Postdoctoral Research Fellowship
Roche Institute of Molecular Biology, 1981 to 1983

PROFESSIONAL ORGANIZATIONS:

American Society for Microbiology
American Association for the Advancement of Science
American Association for Clinical Chemistry

COMMITTEES:

Member of the Hoffmann-LaRoche Research Patent
Coordinating Committee. 1989 to 1991

PATENTS:

INVENTION: A fusion protein comprised of epitopes of the HIV I and HTLV I envelope protein, the corresponding gene, and methods for utilizing the products in Diagnostic Assays.
Patent Application: US/June 10, 1988/US S/N 07/205,401
Inventors: Longiaru, M., Scherer, B., and Terry, R.
Assignee: Hoffmann LaRoche, Inc.

INVENTION: Construction and Expression of Synthetic Genes Encoding Envelope Epitopes of the Human T Cell Leukemia Virus Type I.
Patent Application: October 23, 1989
U.S. Patent 5,837,818 issued November 17, 1998
Inventors: Longiaru, M. and Buonagurio, D.
Assignee: Hoffmann LaRoche, Inc.

INVENTION: Detection of *Chlamydia trachomatis* by Polymerase Chain Reaction using Biotin Labeled Lina Primers and Capture Probes
Patent Application: September 29, 1989
US Patent 5,232,829 issued August 3, 1993
Inventors: Longiaru, M., Silver, S., Sulzinski, M.
Assignee: Hoffmann LaRoche, Inc.

INVENTION: Solid Phase DNA Assays with Protein-DNA Oligomer Conjugates
Patent Application: US/May 3, 1991/US S/N 07/695,072
Inventors: Longiaru, M. and Keys, L.D.
Assignee: Hoffmann LaRoche, Inc.

SELECTED ABSTRACTS:

Longiaru, M., Ikeda, J.E., Jarkovsky, Z., Horwitz, S.B., and Horwitz, M.S. Aphidicolin Inhibits the Replication of Adenovirus DNA. The Imperial Cancer Research Fund Tumor Virus Meeting (SV 40, Polyoma and Adenovirus). Churchill College, Cambridge, England. July, 1979.

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Longiaru, M. Introduction and Update on DNA Probe Technology. The Current Approach to the Laboratroy Diagnosis of Mycobacteria. Industrial Technology Research Institute - Application of DNA Probe in Diagnostic Technology. Taipei, Taiwan ROC March 1-5, 1993.

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ORIGINAL

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99cv2668 H (AJB)

STIPULATION AND ~~[PROPOSED]~~ ORDER ALLOWING GEN-PROBE INCORPORATED TO FILE UNDER SEAL CERTAIN DOCUMENTS UPON WHICH IT RELIES TO SUPPORT ITS MOTION FOR PARTIAL SUMMARY JUDGMENT

I. FACTS

1. On September 18, 2000, this Court entered a Protective Order to govern the use and disclosure of confidential information disclosed in discovery in this litigation, a true and correct copy of that Protective Order and the subsequent amendment thereto are attached hereto as Exhibit A. Pursuant to paragraph 13 of the Protective Order, no documents shall be filed under seal unless the Court issues a separate Order upon application of the affected party.

2. Gen-Probe Incorporated ("Gen-Probe") is now moving for partial summary judgment and among other things relies upon information Defendant Vysis, Inc. ("Vysis") has designated under the Protective Order as being confidential to support that motion.

3. As Exhibit 9 in support of its Motion for Partial Summary Judgement, Gen-Probe relies upon excerpts from the transcript of the deposition of Jonathan Lawrie, Ph.D. taken February 15, 2001. Pursuant to the Protective Order, Vysis designated the transcript of Dr. Lawrie's deposition as Confidential.

4. As Exhibit 10 in support of its Motion for Partial Summary Judgment, Gen-Probe relies upon excerpts of the transcript of the deposition of James Richards, Ph.D. taken March 30, 2001. Pursuant to the Protective Order, Vysis designated portions of the transcript of Dr. Richards' deposition as Confidential-Attorney's Only.

5. The relevant portions of Drs. Lawrie and Richard's deposition transcripts are contained in the sealed envelope attached hereto as Exhibit B and therein are labeled as Exhibits 9 and 10, respectively.

II. STIPULATION

The parties, through their respective counsel, stipulate that the portions of Drs. Lawrie and Richards' deposition transcripts upon which Gen-Probe relies to support its Motion for Partial Summary Judgment shall be filed under seal in accord with the terms of the Protective Order entered in this case.

Dated: April 30, 2001

STEPHEN P. SWINTON
J. CHRISTOPHER JACZKO
COOLEY GODWARD LLP

DOUGLAS E. OLSON
BROBECK PHLEGER & HARRISON LLP

R. WILLIAM BOWEN, JR.
GEN-PROBE INCORPORATED

By: _____
J. Christopher Jaczko

Attorneys for Plaintiff
Gen-Probe Incorporated

Dated: April 30, 2001

CHARLES B. LIPSEY (*pro hac vice*)
THOMAS W. BANKS (195006)
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
THOMAS W. BANKS (195006)

By: Thomas W. Banks
Thomas W. Banks

Attorneys for Defendant
Vysis, Inc.

IT IS SO ORDERED

Gen-Probe may file the excerpts of Drs. Lawrie and Richards' deposition transcripts upon which its relies to support its Motion for Partial Summary Judgment under seal in accord with the terms of the Protective Order entered in this case.

Dated: 5/3/01

JUDGE OF THE DISTRICT COURT

Page 6 of 6

00 SEP 18 AM 9:53

BY Cadenas DEPUTY

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC. Defendants.	CASE NO. 99CV2668 H (AJB) **PROTECTIVE ORDER** Date: September 15, 2000 Time: 9:30 a.m. Dept.: Courtroom A Trial Date: Not Yet Set

WHEREAS, in the course of this litigation disclosure may be sought of information which a party or third party regards as being of a confidential, trade secret, proprietary, technical, commercial, or financial nature (hereinafter collectively referred to as "Confidential Information"); and

WHEREAS, the parties, GEN-PROBE INCORPORATED ("GEN-PROBE") and VYSIS, INC. ("VYSIS") desire to establish a mechanism to protect the disclosure of Confidential Information:

IT IS HEREBY ORDERED that the following shall govern the disclosure of Confidential Information in this action:

1. All originals or copies of transcripts of depositions, exhibits, answers to interrogatories and requests for admissions, and all documents, materials, tangible things and

information obtained by inspection of files or facilities or by production of documents (hereinafter collectively referred to as "Information") which sets forth, refers to, or contains any Confidential Information, may be designated by the party producing the Information either as "CONFIDENTIAL - [producing party's name]" or as "CONFIDENTIAL - [producing party's name] - ATTORNEYS ONLY" (i.e., "CONFIDENTIAL – GEN-PROBE - ATTORNEYS ONLY" or "CONFIDENTIAL - VYSIS - ATTORNEYS ONLY.").

2. Any Information designated as CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY and all Information derived therefrom (excluding such Information as is derived lawfully from an independent source), shall not be disclosed to anyone except as provided in Paragraphs 3, 4 and 5, below, shall be used only for the purposes of this litigation, and shall not be used for any business, financial or other purpose whatsoever.

3. Information designated as CONFIDENTIAL shall not be given, shown, made available or communicated in any way to any person or entity other than the following:

(a) Lawyers for Gen-Probe:

(i) Cooley Godward LLP

(ii) R. William Bowen, Jr.

(iii) Peter R. Shearer

(iv) Christine A. Critzmacher

(b) Lawyers for Vysis:

(i) Finnegan, Henderson, Farabow, Garrett & Dunner LLP

(ii) Wright & L'Estrange

(iii) Norval B. Galloway

(c) Partners, members, associates, or employees of any of the foregoing lawyers assisting in this litigation;

(d) The Court and Court personnel and stenographic reporters at depositions taken in this action;

(e) The following individuals:

(i) Officers, directors and up to three designated employees of GEN-PROBE; **PROVIDED, HOWEVER**, that GEN-PROBE must designate such employees and give notice to VYSIS of such designation not later than 10 days prior to the disclosure of any **CONFIDENTIAL** Information to such person;

(ii) Officers, directors and up to three designated employees of VYSIS; **PROVIDED, HOWEVER**, that VYSIS must designate such employees and give notice to GEN-PROBE of such designation not later than 10 days prior to the disclosure of any **CONFIDENTIAL** Information to such person:

(f) Independent experts or consultants whose substantive advice is or will be used by a party hereto in connection with preparation for trial or trial of this action, as well as any employees, associates or independent contractors retained by those experts to assist in their work on this matter. Counsel desiring to disclose **CONFIDENTIAL** or **CONFIDENTIAL - ATTORNEYS ONLY** Information to such experts or consultants shall first obtain a signed undertaking, in the form of Exhibit A attached hereto, from each such expert or consultant. Such Information will not be disclosed to any such expert or consultant for a period of ten (10) days after service by facsimile, Federal Express or other next day mail of the signed undertaking upon opposing counsel. Proposing counsel shall also provide opposing counsel with information regarding the identities of the proposed experts or consultants, including their names, address and job titles, the name and addressees of their employers and a current curriculum vitae including a list of all persons or entities for whom such persons consulted or from whom they received income directly or indirectly during the prior four (4) years:

(g) Any person that originally authored or received the document, or gained knowledge of the Information it contains in the regular and ordinary course of business; and

(h) Independent contractors retained to assist with non-substantive aspects of the preparation for trial or trial of this litigation (e.g., copying services, graphics services, jury consultants, etc.).

4. Information designated as CONFIDENTIAL - ATTORNEYS ONLY shall not be given, shown, made available or communicated in any way to any person or entity other than those persons described in paragraphs 3(a), 3(b), 3(c), 3(d), 3(f), 3(g), and 3(h) above.

5. Third party discovery in this proceeding may involve disclosure of Confidential Information, which if designated in conformity with the provisions of this Order, shall be subject to the provisions herein and provide the non-party with all of the rights and obligations set forth herein. In order to expedite third party discovery, a copy of this Order and a letter generally informing the third party of its right to invoke the protections set out herein shall be served with all such discovery.

6. In the event that a producing party inadvertently fails to designate Information CONFIDENTIAL or CONFIDENTIAL ATTORNEYS ONLY or incorrectly so designates Information, that party may make a late designation or change the designation by so notifying in writing all parties to whom the Information has been disclosed. The receiving parties shall take reasonable steps to ensure that the Information is thereafter treated in accordance with the designation. Late designation shall not be deemed a waiver of the confidential status of the late designated Confidential Information. No person or party shall incur any liability hereunder with respect to disclosure that occurred prior to the receipt of written notice of belated designation.

7. If an opposing party desires to object to the submission of CONFIDENTIAL or CONFIDENTIAL ATTORNEYS ONLY Information to individuals identified in paragraph 3(f), it shall notify the proposing party in writing and by facsimile transmission (with original sent by First Class Mail), within the ten (10) day period referred to in paragraph 3(f) of its objection and the

grounds therefore. If no such objection is made in such time and manner, the proposing party may disclose CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY Information to such person subject to the subsequent provisions in this paragraph. If an objection is properly made and the dispute is not resolved on an informal basis between the proposing and objecting party, the proposing party shall, within twenty (20) days after such written objection, submit the matter on motion to the Court for ruling. In the event of such written objection, the proposing party shall withhold disclosure of CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY Information to the objected individuals pending the ruling of the Court or written agreement between the parties to the dispute.

8. The attorneys of record shall maintain a file of all written agreements signed by persons to whom they have given materials designated as CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY. Said file shall be made available upon request for inspection and copying by any attorney of record.

9. Counsel shall not disclose Information designated as CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY to a witness testifying at a deposition except in strict conformity with the provisions of this Order. No such disclosure shall be made to any witness unless that witness is entitled by this Order to receive that Information or the party that produced that Information assents to the disclosure of such Information in writing or on the record of the deposition. If, during the course of any deposition, (a) an attorney of record for any party desires to make inquiry into Information subject to the designation CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY, or (b) an attorney of record for a party asserts that an answer to a specific inquiry is subject to the foregoing designations, the attorney shall make such inquiry only in the presence of those persons authorized access to such Information. Such testimony shall be sealed, and the parties hereto shall treat it subject to the provision for disclosure set forth herein. Nothing in this paragraph shall preclude counsel at a deposition of a party witness from disclosing to the party witness confidential information produced by that party.

10. All testimony elicited during depositions, hearings, and other proceedings shall be deemed **CONFIDENTIAL – ATTORNEYS ONLY** until the expiration of thirty (30) days after the mailing or after delivery of a copy of the transcript of the testimony by the court reporter to counsel who requested a copy of the transcript. This paragraph will not otherwise affect the deposition, hearing or other proceeding which is being recorded while it is in session. Within the thirty-day period following such mailing of the transcript, any party may, by written notice served on all parties, designate all or any portion of the testimony to be **CONFIDENTIAL** or **CONFIDENTIAL - ATTORNEYS ONLY**. The right to make such designation shall be waived unless made before the end of the thirty-day period. Upon being informed that certain portions of a transcript are designated as **CONFIDENTIAL** or **CONFIDENTIAL - ATTORNEYS ONLY**, each party must cause each copy in their custody, possession or control to be so marked immediately.

11. Any court reporter who transcribes testimony in this action at a deposition shall agree, before transcribing any such testimony, that all **CONFIDENTIAL** and **CONFIDENTIAL - ATTORNEYS ONLY TESTIMONY** is and shall remain confidential and shall not be disclosed except as provided under this Order and that copies of any transcript, reporter's notes or any other transcription records of any such testimony shall be retained in absolute confidentiality and safekeeping by such shorthand reporter or shall be delivered to an attorney of record or filed with the Court.

12. Interrogatory answers and answers to requests for admissions designated as **CONFIDENTIAL** or **CONFIDENTIAL - ATTORNEYS ONLY** shall be delivered to the attorney of record propounding the interrogatories or requests without being filed with the Court unless required in any further proceedings herein. When documents so designated and/or other matters of the same or similar nature are the subject of inquiry at depositions, the portion of the transcript which sets forth or contains Information about such, together with such documents, shall be sealed and shall not be filed with the Court unless required in any further proceedings herein.

13. No Information that was designated previously as **CONFIDENTIAL** or **CONFIDENTIAL - ATTORNEYS ONLY** will be filed with the Court unless it is filed under seal. To

comply with this requirement, CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY Information must be filed in sealed containers labeled with: (1) the title to this action; (2) the general nature of the contents; (3) the words CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY; and (4) a statement substantially in the following form:

> CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER. This sealed container filed in this case. *Gen-Probe Incorporated v. Vysis, Inc.*, United States District Court, Southern District of California Case No. 99cv2668II (AJB), contains confidential materials, which may be used only in connection with the prosecution or defense of this lawsuit. Pursuant to Protective Order, the container shall not be opened nor the contents thereof revealed except to the Court. After any such opening or revelation, the container shall be resealed with the contents inside.

Nothing shall be filed under seal, and the court shall not be required to take any action, without separate prior order by the judge before whom the hearing or proceeding will take place, after application by the affected party with appropriate notice to opposing counsel.

14. Should an attorney of record for any party desire to use Information designated as CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY, or any summary thereof or excerpt therefrom, during the trial of or at any hearing in this action, counsel shall, prior to such use, bring the confidentiality thereof to the attention of the Court and/or the party which designated the Information. Counsel for the producing party may request that any portion of the transcript or exhibit containing such Information be filed under seal with the Court, and be accorded protection as provided by the terms of this Order. All persons present at the time of such use shall be directed to treat such Information as Confidential Information, and counsel for the parties shall exercise all reasonable care not to disclose such materials needlessly in the public record of this proceeding nor to persons not entitled under this Order to receive such Information.

15. The designation by counsel for the disclosing party of any Information as constituting Confidential Information is intended solely to facilitate the preparation and trial of this case, and such designation shall not be construed in any way as an admission or agreement by any

party that the designated disclosure constitutes or contains any Confidential Information in contemplation of law.

16. Within sixty (60) days of the final disposition of this action, whether by judgment (including exhaustion of all appeals), settlement or otherwise each attorney of record shall promptly deliver to the party or witness from whom obtained either (1) all items which have been marked CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY and all copies made thereof or (2) an affidavit sworn under penalty of perjury declaring that all such items and all copies thereof have been destroyed. However, the law firm of each attorney of record may retain one record copy of any items filed with the Court upon notice to the other attorneys of record of such retention and subject to the terms of this Order.

17. If a party desires to object to the designation of CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY as applied to specific Information, it shall serve its objections in writing and by facsimile transmission (with original sent by First Class Mail). If the objections are not resolved on an informal basis between the designating party and the objecting party, the objecting party may, within twenty (20) days after service of such written objection, submit to the Court for ruling a noticed motion to be relieved entirely or in part from the provisions of this Order.

18. In the event anyone shall inadvertently disclose Information another party or third party has designated CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY, the party making the inadvertent disclosure shall, upon learning of the disclosure:

(a) Promptly notify the person to whom the disclosure was made that the disclosure contains Confidential Information;

(b) Promptly make all reasonable and necessary efforts to obtain the return of and preclude dissemination or use of the Confidential Information by the person to whom disclosure was inadvertently made; and

(c) Immediately notify the producing party of the identity of the person to whom the disclosure was made, the circumstances surrounding the disclosure, and the steps that

have been taken and will be taken to ensure against further dissemination or use of the Confidential Information.

19. In the event anyone shall violate, or threaten to violate, any terms of this Order, the parties hereto agree that the aggrieved party may immediately apply to obtain injunctive relief against any such person, and in the event the aggrieved party shall do so, the respondent person, subject to the provisions of this Order shall not employ as a defense thereto or claim that the aggrieved party possesses an adequate remedy at law.

IT IS SO ORDERED.

Dated: _____

_____
JUDGE OF THE DISTRICT COURT

EXHIBIT A

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC., Defendant.	No. 99cv2668 H (AJB) UNDERTAKING

I, _____, declare and say that:

1. I _____ live at _____ _____ _____ _____ _____ _____.

2. I am employed as _____ by _____ _____ _____.

3. I have read the Protective Order entered *Gen-Probe Incorporated v. Vysis, Inc.*, Case No. 99cv2668 H (AJB), and a copy of the Protective Order has been given to me.

4. I agree to be bound by the terms of the Protective Order, and agree that any information designated as CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY within the meaning of the Protective Order, will be used by me only to assist counsel in connection with the above-referenced litigation.

5. I agree that I will not disclose or discuss Information designated as **CONFIDENTIAL** with anyone other than the persons described in Paragraph 3 of the Protective Order.

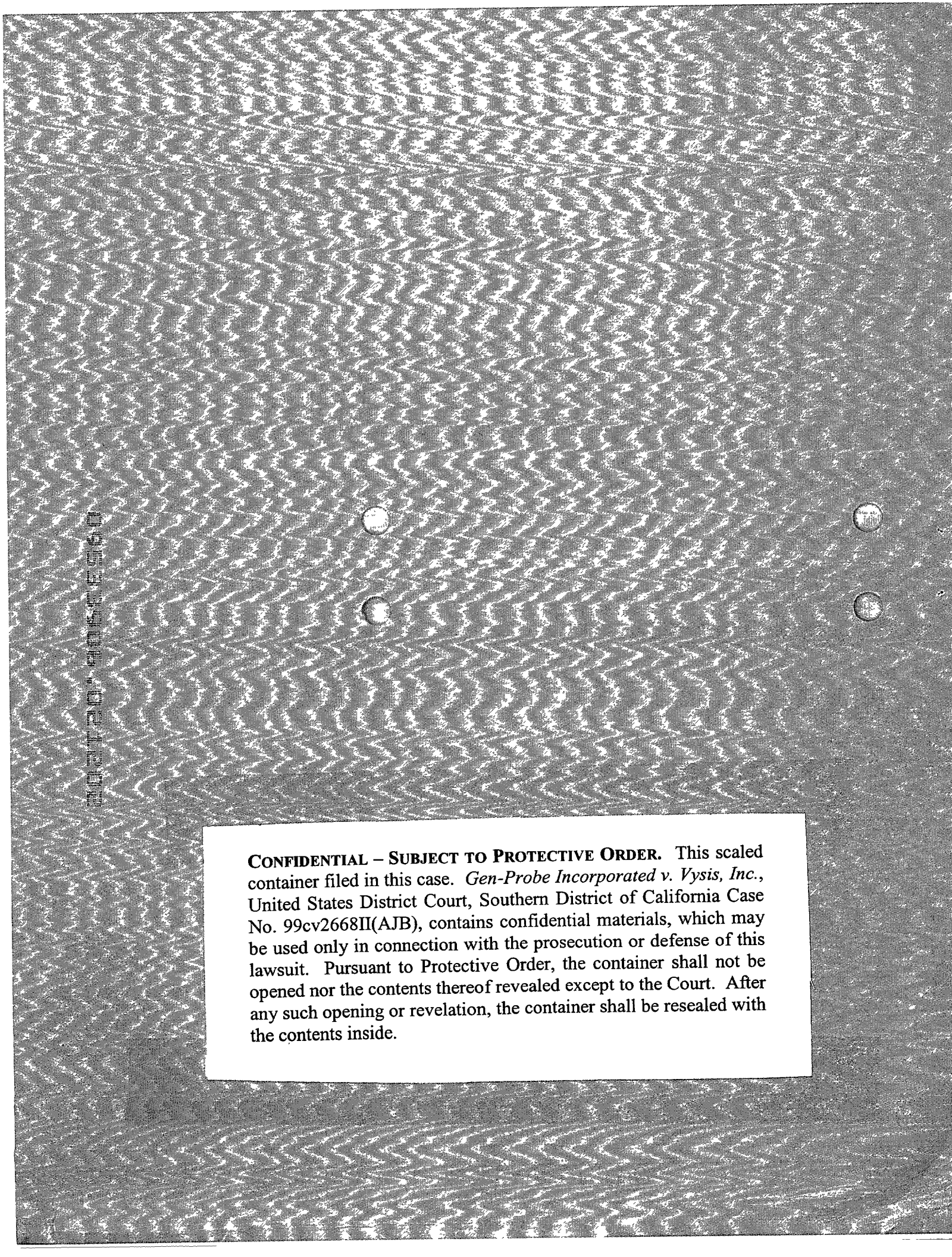
6. I agree that I will not disclose or discuss Information designated as **CONFIDENTIAL - ATTORNEYS ONLY** with anyone other than the persons described in paragraph 4 of the Protective Order.

7. I understand that any disclosure or use of Information designated as **CONFIDENTIAL** and **CONFIDENTIAL – ATTORNEYS ONLY** in any manner contrary to the provisions of the Protective Order will subject me to sanctions for contempt of the Court's Order.

8. I agree to be subject *in personam* to the jurisdiction of the United States District Court for the Southern District of California in connection with any proceeding relating to the enforcement of the Protective Order.

I declare under penalty of perjury that the foregoing is true and correct and that this declaration was executed this _____ day of _____, 2000, at _____.

_____



CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER. This scaled container filed in this case. *Gen-Probe Incorporated v. Vysis, Inc.*, United States District Court, Southern District of California Case No. 99cv2668II(AJB), contains confidential materials, which may be used only in connection with the prosecution or defense of this lawsuit. Pursuant to Protective Order, the container shall not be opened nor the contents thereof revealed except to the Court. After any such opening or revelation, the container shall be resealed with the contents inside.

Exhibit 9 has been filed under seal under separate cover

IN THE UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

- - - - - - - - - - - - - - -X

GEN-PROBE INCORPORATED,

Plaintiff,

VS.

VYSIS, INC.,

Defendant.

- - - - - - - - - - - - - - - X

NO.99cv2668 H (AJB)

CONFIDENTIAL

Videotaped Deposition of
JONATHON MICHAEL LAWRIE, Ph.D.
Durham, North Carolina
Thursday, February 15, 2001

Reported by:
Sydney C. Silva, Registered Professional Reporter
File No:

COPY

Ex. 9 Pg. 45

A. No. 14:34:16

Q. Do you know whether there's any reference in the patent to a combination of target capture with a target-specific method of application -- of amplification? 14:34:17 14:34:19 14:34:25 14:34:26

A. This patent here? 14:34:27

Q. Yes. 14:34:29

A. I haven't read it completely, just the pieces you have shown me. 14:34:29 14:34:32

Q. When the patent application was filed, did you have any impression about whether the greatest degree of specificity sensitivity might be obtained by combining target capture with a target-specific method of amplification? 14:34:34 14:34:36 14:34:38 14:34:42 14:34:47

A. I don't remember. 14:34:56

Q. Does that stand to reason at all? 14:34:56

A. I don't think so. I don't know what the thought process would have been back then. 14:34:58 14:35:00

Q. Can you recall any reason that a reference to PCR might have been intentionally omitted from the patent application? 14:35:03 14:35:05 14:35:08

A. Yes. 14:35:15

Q. And what reason was that? Let me, let me start over. 14:35:15 14:35:23

Ex. 9 Pg. 46

Was a reference to PCR intentionally omitted from the patent to the best of your understanding? 14:35:24 14:35:27 14:35:29

A. I don't know. 14:35:30

Q. Were there discussions about whether or not to include a reference to PCR in the patent? 14:35:31 14:35:32

A. I can't remember. 14:35:36

Q. So at Amoco you had a thought about combining target capture with PCR, is that right? 14:35:47 14:35:51

A. Yes. 14:35:54

Q. Gene-Trak then did work in an effort to combine target capture with PCR, is that right? 14:35:55 14:35:58

A. From seeing this here, yes. 14:36:03

Q. Do you have a recollection of that? 14:36:05

A. No. 14:36:07

Q. If there's no reference in the patent to combining target capture with PCR, do you have any explanation as to why it is not there? 14:36:07 14:36:09 14:36:13

A. I believe that it was a separate -- the thought behind this was coming up with new methods of amplification, not old ones. 14:36:15 14:36:17 14:36:19

Q. And you would, for the purposes of what you just said, you classify PCR as an old method of amplification? 14:36:31 14:36:32 14:36:36

A. PCR itself was described in the patent, yes, issued patent. 14:36:37 14:36:40

Q. And your understanding of the 338 patent was that it was directed to other methods of amplification? 14:36:41 14:36:44 14:36:47

A. The, it was, it was directed to the methods disclosed by, you know, the methods separate from PCR. 14:36:48 14:36:54 14:36:59

Q. Those being the methods, for example, as the methods set forth in Example 6 and 7? 14:37:07 14:37:10

A. Yes. 14:37:14

Q. Is it your understanding that the 338 patent then doesn't encompass the combination of target capture and PCR? 14:37:20 14:37:22 14:37:28

MR. BANKS: Object to the form. 14:37:30

A. I couldn't say. 14:37:31

Q. I'm sorry? 14:37:32

A. I couldn't say. 14:37:32

Q. Was it your intention that it encompass the combination of target capture and PCR? 14:37:33 14:37:38

A. I don't know. I can't remember what the intention was in regards to PCR. 14:37:40 14:37:41

Q. However, your recollection of why -- of if there's no -- your explanation of why there 14:37:49 14:37:50

might not be a reference to PCR in the patent is that the patent wasn't intended to cover old methods of amplification such as PCR; is that right? 14:37:53 14:37:56 14:38:03 14:38:06

A. The patent was intended to cover the discoveries by myself, Halbert and King that there should be in some, you know, disclosure back at Amoco. That's what the patent was about. 14:38:07 14:38:09 14:38:15 14:38:16

why PCR was left out I can just speculate. It wasn't what we came with, it was in the previous, it was a previous older method. 14:38:22 14:38:26 14:38:30

Q. You were looking for other things? 14:38:33

A. Yeah. 14:38:36

MR. BOWEN: Let's assume that the patent application for the 330 patent was filed on December 21, 1987. Can we stipulate to that? 14:39:04 14:39:06 14:39:10

MR. BANKS: For which patent? 14:39:16

MR. BOWEN: The 330. 14:39:18

MR. BANKS: The 330? Moving to a different one now? 14:39:20 14:39:21

MR. BOWEN: I'm confused this late in the day, huh? The first application that claimed the combination of target capture and amplification. 14:39:22 14:39:25 14:39:27 14:39:32

Ex. 9 Pg. 49

Example 5 is a linear method? 16:21:41

A. Let's see. 16:21:44

Yes, it is linear. 16:22:29

Q. So Example 5 discloses a linear nonspecific method of amplification? 16:22:31 16:22:34

A. Yes. 16:22:37

Q. So recapping the examples, Examples 1 through 3 disclose capture methods without amplification? 16:22:38 16:22:43 16:22:46

A. Yes. 16:22:48

Q. And Example 4 discloses linear nonspecific amplification? 16:22:49 16:22:53

A. Yes. 16:22:54

Q. Example 5 discloses linear nonspecific amplification? 16:22:55 16:22:59

A. Yes. 16:23:00

Q. Example 6 seeks to describe nonspecific exponential amplification? 16:23:02 16:23:10

A. Let's see. Yes. 16:23:13

Q. And Example 7 describes -- seeks to describe nonspecific exponential amplification? 16:23:18 16:23:22

A. Yes. 16:23:28

Q. Looking back at Column 30, specifically at Lines 30 through 40, which I think is two 16:23:44 16:23:48

Exhibit 10 has been filed under seal under separate cover

CONFIDENTIAL - ATTORNEYS' EYES ONLY

VOLUME: I

PAGES: 1-191

EXHIBITS: 115-132

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

- x

GEN-PROBE INCORPORATED,

Plaintiff,

v. C.A. No.

VYSIS, INC., 99CV2668 H (AJB)

Defendant.

- x

CONFIDENTIAL - ATTORNEYS' EYES ONLY

DEPOSITION of JAMES C. RICHARDS

March 30, 2001

9:51 a.m.

Westin Hotel

70 Third Avenue

Waltham, Massachusetts

Reporter: Michael D. O'Connor, RPR

Ex. 10 Pg. 51

Plaintiff in the case is Gen-Probe Incorporated and the Defendant in the case is Vysis, Inc.

Do you understand that Vysis is the successor to Gene-Trak Systems?

A. Yes.

Q. Let's discuss your educational background briefly. Vysis has produced some documents in the case which lead me to believe that I know something about your background, but I'd like to confirm it.

Did you obtain a Bachelor of Science in microbiology and chemistry from the University of Illinois?

A. Yes.

Q. When did you graduate?

A. 1970.

Q. Did you obtain a Ph.D. in microbiology and biochemistry from Southern Illinois University?

A. Yes.

Q. When did you obtain that degree?

A. '78, '79.

Q. And after you obtained your Ph.D. from Southern Illinois University, did you do

Q. Do you recall when you left DuPont to go to work for Amoco?

A. Yes.

Q. When was that?

A. December, '84, January, '85; that was the time. I don't know when I left. I think it was before Christmas of '84, but I can't remember exactly.

Q. When you joined DuPont you became program manager for the nucleic acid probe development group?

A. Excuse me, which company?

Q. When you joined Amoco --

A. Amoco, yes.

Q. -- in December of '84, January of '85, you became program manager for the nucleic acid probe development group?

A. I left DuPont December, '84. I started at Amoco February 1 of '85.

Q. Thanks. At that time what job --

A. Program manager, DNA probe development.

Q. Did you stay in that position with Amoco until you left for Gene-Trak?

A. Yes.

Q. You left for Gene-Trak sometime in 1986?

A. Roughly October, '86.

Q. So you were at Amoco from February of '85 to October of 1986?

A. Correct.

Q. While you were program manager of the nucleic acid probe development group at Amoco, what kind of work did you or your group do?

A. I was alone and I wrote the business plan for DNA probes for Amoco.

Q. When you say you were alone, there weren't people that reported to you?

A. No. Oh, wait a minute. Time out. I can't remember if Bach and Ryan and the engineers reported to me or Lawrie. It doesn't matter. I was doing business development.

Q. I'd like you to look at Exhibit 38, which aught be the next one in the book behind the '338 patent, which is an organizational chart. This organizational chart has been previously marked in the case as Exhibit 38. It appears to be --

A. Oh, I had sample prep, that's right, and I had the engineers I guess.

MR. BANKS: Let him ask the questions.

A. I'm sorry. I don't remember.

Q. This appears to be an undated organization chart related to the DNA probe effort at Amoco. To the best of your recollection, does this chart, Exhibit 38, reflect the organization of the probe group in 1986?

A. Yes.

Q. Can you tell from looking at this chart who reported to you or does it refresh your recollection?

A. I will tell you, now I remember. Kessler was doing sample prep, and Bach and Ryan in the engineering group were doing the system, and they loosely reported to me. I don't remember Halbert and Dudzik. I thought they reported to Lawrie. The rest of this was all Lawrie. That's why I say, I was working on business development for the most part, and the only reason Bach and Ryan reported to me because I knew them at DuPont, and I hired Jack from

putting enzymes on Mark's target capturing method, removing noise, and generating a higher signal. So we used target capture and signal amplification, i.e., using the ELISA type approach. But we were also doing radioactive labels, and we were, of course, all aware of other things that were out there.

Q. Do you know who at Amoco had the original idea to combine target capture and some form of amplification?

A. It might have been Mark, but I don't remember.

Q. While you were at Amoco, did you ever have the understanding that Collins, King, Halbert and Lawrie had conceived of an invention that involved the combination of target capture and amplification?

A. John mentioned it to me once.

Q. What did he tell you, that you can remember.

A. Well, in writing the business plan, I was always concerned about rare targets, and one day John came into my office -- we were right down the hall at Amoco from each other -- and he

said, we've got a way to make more targets, and he described the method, and I didn't understand the method, because I had never used it in my research, and it was Klenow and some other stuff.

He explained you could do this in a way to make more target, and I said, what about PCR? He said, You could do PCR, but you could also use this, and I said, Well, okay. Sounds good to me, and off he went. That was it. I mean, we didn't pursue it, because we had a clear business structure, and it was target cycling, and an enzyme label, and we were going to go do this new business, and I said, Well, when you get it proven, come and see me basically.

Q. In part of your statement you used the term "rare targets." By that term are you referring to targets that are in a sample in low concentration?

A. Right.

Q. Did you ever have an understanding about how this invention was conceived, whether it was at a brainstorming meeting?

Gene-Trak deal.

Q. Do you remember that the first article on PCR was published in "Nature" in about December, 1985?

A. No, I don't remember that.

Q. When the first article describing PCR was published, was it big news?

A. Yes.

Q. After that article was published, did other people in the industry outside Cetus begin looking for alternative ways to do the same thing?

MR. BANKS: Objection to form.

A. Do I know if they were?

Q. Right.

A. I don't know.

Q. Do you know whether Amoco started to think about what it could do that would be similar to PCR?

A. Amoco owned 25 percent of Cetus at that time, and discussions were running around should we take a license to this, because we owned 25 percent of the company, and that was the extent of the discussion, and that was way

did you live in the Chicago area?

A. '85 to '86, and I lived in Lisle.

Q. Outside of Chicago?

A. Next to Naperville about 100 feet or so; very close, next door.

Q. And when you went to work for Gene-Trak in about October of '86, did you move to the Boston area?

A. Framingham.

Q. Did Halbert, King, Collins and Lawrie also move from Amoco to Gene-Trak?

A. Yes, I believe so.

Q. Prior to the time that Gene-Trak was formed, were you involved in discussions or negotiations concerning the value of the respective contributions that were being made by Amoco and Integrated Genetics?

A. Me involved in the valuation? I don't remember.

Q. Were you involved in the negotiations between Amoco and Integrated Genetics?

A. No. No, as an absolute. Gar Royer and Ed Mason were the main Amoco, I believe, people involved in the face-to-face

A. Yes.

Q. About the same time?

A. About the same time.

Q. And he is shown here as being the manager of scientific affairs?

A. Yes.

Q. In that position, what did he do?

A. He was going to be in charge of clinical trials, setting up the ways -- actually, his primary responsibility was to set up what we called our clinical reference laboratory, where we were going to bring in real clinical samples from patients to do probe capture of pathogens, and it had to be a BL-3 lab, a containment facility. It was literally a full-time job just doing that. We set it up in a separate building.

Q. And as director of business development and licensing at Gene-Trak, what were your responsibilities?

A. Licensing technology, licensing in, licensing out, if we could. If R&D needed something, go out and find it, basically if they needed a new technology, go out and get a

license, constantly assessing the business plan, are we on target, setting milestones, assisting Connoy with the budget, making sure we were achieving our milestones. It's what business development is.

Q. So part of your job was dealing with the technology assets and the technology needs of R&D?

A. Yes, I think that's fair.

Q. Now, the technology assets of a company are sometimes referred to as intellectual property?

A. IP, yes.

Q. IP includes things like patents, trademarks, confidential business information?

A. Mostly in my case it was patents, memoranda of invention, trademarking, I guess, but it was handled mostly by the attorneys.

Q. When you say "patents," that would include issued patents and it would include pending patent applications?

A. In this case, I can tell you it was almost exclusively what we were inventing at Gene-Trak in the form of MOIs, and having them

Q. And you were on that committee?

A. Correct.

Q. And the committee established priorities for filing patent applications based on the memorandum of invention?

A. Not completely. I mean, it had to have a business value. I mean, that's why I was there. Is this going to help us meet our milestones, or is this just extra stuff, but we aren't using it, so therefore, we've got to be working on the things that we need for commercialization. So there's business criteria is how you prioritize these.

Q. So would the patent committee both look at the science of a memorandum of invention and the business application of that science?

A. As it pertained to our existing milestones.

Q. While you were at Gene-Trak, were you involved in any out-licensing activities?

A. I don't remember.

Q. While you were at Gene-Trak, were you involved in any in licensing?

A. Yes.

Q. So in licensing would take place if some other company had technology or intellectual property that Gene-Trak was interested in using in its business?

A. Not just companies, but, yes. It could be universities, whatever. Somebody else owned it.

Q. If somebody else had some technology --

A. That we might need.

Q. -- that Gene-Trak thought might be useful, you would get involved in trying to license that technology for Gene-Trak?

A. Yes.

Q. Did Dr. Klinger get involved in licensing activities?

A. Yes.

Q. Were you involved in the negotiation of most of the licenses that Gene-Trak took?

A. Involved, yes.

Q. Were you involved in evaluating technologies that Gene-Trak was looking at to license?

A. Yes.

Ex. 10 Pg. 63

There were others, other methods.

Q. There were other methods?

A. (Witness nods).

Q. There were other sequence specific methods before PCR?

A. Before PCR? I don't know the timing, but Salk, and there were others.

Q. Looking at Exhibit 45, if a presentation was made to the partnership committee meeting on patents in the summer of '87, is it likely that you made the presentation?

A. Yes.

Q. And if a presentation was made on nucleic acid amplification strategy, is it likely that Dr. Lawrie made the presentation or would you have made it?

A. It probably would have been me. This looks like it would have been me.

Q. Is there anything here that tells you it would have been you or suggests to you it would have been you?

A. Yes, because it looks like it came off of my Macintosh computer, the type. I recognize

of doing nucleic gymnastics. Discrete date, no. I don't have any discrete date or time. It was an ongoing intellectual discussion.

Q. I'd like you to look at, I think it's the fourth page of this pack of schematics, Exhibit 49. It's got a No. 4 in the upper left-hand corner, and it talks about specific capture, apparently followed by nonspecific amplification, and then another specific capture step. Do you see that?

A. Yes.

Q. Did you understand this to be the method that Dr. Lawrie had discussed with you, the Collins method?

A. Do you mean not looking at this?

Q. Right.

A. Yes. Again, the hexadecamer, Klenow, yes, that's what I remember.

Q. Hexadecamer, when you use that term, are you referring to a hexamer primer?

A. It was the one you could buy from commercial sources. They were, I think, random.

Q. So when you're using the term "hexadecamer primer," you're referring to a

commercially available random hexamer primer?

A. That was my understanding of the nonspecific amplification concept.

Q. And that was what you understood Dr. Lawrie to have talked to you about?

A. Among others, yes.

Q. The fourth thought here on the fourth page of Exhibit 49 is a question, "Too close to Cetus." Do you see that?

A. Yes.

Q. Do you have any recollection of there being concern at Gene-Trak that the method of doing specific capture in conjunction with nonspecific amplification might be too close to the PCR method?

A. I don't remember that. This is not my thing. Somebody else did this stuff.

Q. I'd like you to look at what's previously been marked as Exhibit 53, if you would. Exhibit 53, the first page of Exhibit 53 is entitled, "Partnership Committee Meeting, January 23, 1987." Item 7 on the list is "Patent Strategy," and your name appears opposite that.

Ex. 10 Pg. 66

him?

A. Yes.

Q. When presentations on patents were given to the partnership committee, is it your recollection that you gave those presentations?

A. Yes.

Q. Was there a reason that you gave the presentations and not Mr. Janiuk or Mr. Hofer?

A. I don't believe I gave patent presentations. I think I talked about the business implications of what they might reflect. I didn't and don't understand claim language, then or now. I used to mess it up. So I stuck pretty much to the business relationship between the patent and claims and what we were trying to accomplish. I just stuck to the business.

Q. I'd like you to look back at Exhibit 45, please.

A. Yes.

Q. I think you said when we looked at Exhibit 45 before that you're probably the author of Exhibit 45?

A. Yes.

Ex. 10 Pg. 67

A. Yes.

Q. In Step 3A there's a reference to hexamer primers?

A. Yes.

Q. And I think this morning you told me that you would generally consider the reference to hexamer primers to commercially available random hexamer primers?

A. As I understood it, yes.

Q. In looking at that term here and remembering the language that we just looked at in Column 15 about nonspecific amplification, do you understand that reference to hexamer primers to be a reference to random hexamer primers in Figure 5?

A. Well, if they are random hexamer primers, yes, I guess that would be what I was led to believe.

Q. Random hexamer primers would be used in nonspecific amplification?

A. Right. That's what John had led me to believe back when.

Q. Turning to Figure 6, again, in Step 3A, there's a reference to hexamer primers. Do

specially tailored primers are needed, do you have any understanding why someone would then use specific primers?

MR. BANKS: Object to form.

A. You would want to use any kind you could, not just specific, nonspecific; anything. You would want all aspects.

Q. Looking at example four, the last paragraph, which is in Column 31, about Line 16 --

A. I'm sorry, repeat where the location is?

Q. About Line 16 of Column 31.

A. Okay.

Q. There's a reference there to the resulting nonspecific transcription. Do you see that?

A. Yes.

Q. Example five, the first paragraph, do you see that it refers to nonspecific replication?

A. Oh, I see it.

Q. Is it your understanding that example five is describing a method in which nonspecific

primers are used?

MR. BANKS: Object to form.

A. That's what it says, I think.

Q. The same with example six. Do you see in example six, which is Column 31, at about Line 63, the example refers to the use of random hexamer primer oligonucleotides?

A. Right.

Q. Example six is a method describing nonspecific primers?

MR. BANKS: Object to form.

Q. Is that correct?

A. I'm reading it, yes.

Q. And example seven, which is Column 32, at about Line 13, it talks about replicating nonspecifically. Do you see that?

A. What it says is it's a precise transcript is purified. I'm reading it, but I'm not sure in this case what the specificity is imparted. The hybrid duplex is then denatured. I can read. I'm not sure what the -- I have to look at the -- is there a figure for this?

Q. I don't think that there is.

A. It sounds like there's specificity

involved in the capture probe. I'm sorry, what's the question in No. 7?

Q. Is it your understanding that the amplification step in example seven uses nonspecific primers?

A. Does it use nonspecific primers? It appears that's what it says.

Q. So when we look at examples five, six and seven, all of them use nonspecific primers in the amplification step?

A. In some aspect.

MR. BOWEN: Take a five-minute break.

VIDEOGRAPHER: Off the record. The time is 2:04.

(Recess)

VIDEOGRAPHER: Back on the record. The time is 2:17.

BY MR. BOWEN:

Q. Dr. Richards, when you were at Gene-Trak, did you ever have an understanding that Gene-Trak, as an organization, thought that using random primers and target capture might be a method that was more suitable for automation than PCR?

patents to the partnership committee, the management committee of Gene-Trak, you were the person who made the presentations?

MR. BANKS: Object to form.

MR. BOWEN: What don't you like about it?

MR. BANKS: Lack of foundation.

MR. BOWEN: Okay.

Q. When presentations on patents were made to the partnership committee, did you make the presentations?

A. Yes.

Q. And you did that about once a quarter?

A. Yes.

Q. You had been on the patent committee? By December of 1989, you had been on the patent committee for Gene-Trak for a number of years?

A. Yes.

Q. You had access to and discussed patent matters with Gene-Trak's patent counsel?

A. Yes.

Q. You discussed the application for the '338 patent with Gene-Trak's patent counsel?

A. I don't remember.

Ex. 10 Pg. 72

Q. You made presentations on target capture patents to the scientific advisory board of Gene-Trak?

A. Yes.

Q. Let me show you what we will mark as Exhibit 121, which is a document entitled at the top "Business Development, August 3, 1988."

Do you believe you prepared Exhibit 121?

(Document marked as Exhibit 121 for identification)

A. I believe so, yes.

Q. Exhibit 121 is an evaluation of patents and licenses?

A. Yes.

Q. You evaluated these technologies as part of your job as director of business development and licensing?

A. Yes.

Q. In December, 1989, what were your sources of understanding about what the pending patent application for the technology that's covered by the '338 patent was about? What were your sources of information for your

understanding?

A. What date?

Q. December, 1989.

A. What was my understanding?

Q. As of December, 1989, did you have an understanding about what technology was covered by the '338 patent?

A. Yes.

Q. What were your sources of information for that understanding?

A. My recollection of my conversations with John years before, and just simply a nonspecific way of amplifying.

Q. I will show you what we will mark as Exhibit 131 to your deposition. Last week, did you remember writing a letter to Dr. Orgell in December, 1989 concerning the subject matter of the '338 patent?

(Document marked as Exhibit 131 for identification)

A. Last week?

Q. Yes.

A. I do not remember seeing this until I saw it the other day.

Ex. 10 Pg. 74

Dr. Orgell --

A. Orgell.

Q. -- Amoco was a partner in Gene-Trak?

A. Yes.

Q. Amoco owned half of Gene-Trak; is that right?

A. A large percentage. I don't remember how much.

Q. And Dr. Orgell was the general manager of research at Amoco Technology?

A. Yes.

Q. In the corporate ladder, is Dr. Orgell up the ladder from you?

A. Oh, yes. He's Amoco. I was not in Amoco.

Q. He worked directly at Amoco?

A. No. I was a Gene-Trak employee.

Q. Amoco owned half of Gene-Trak?

A. Yes.

Q. Did you consider Dr. Orgell, in any sense, to be one of your bosses?

A. I considered him like a venture capital -- I mean, he's a finance -- he's one of the people that bankrolls the company, and a guy

I have to convince to pursue technology.

Q. Looking at the people who received ccs of this letter, Patrick Connoy was your boss at Gene-Trak?

A. Yes.

Q. Dr. Royer was another bigwig at Amoco Technology?

A. He was my boss at Amoco.

Q. He was on the Gene-Trak scientific advisory board?

A. Yes.

Q. He had been at scientific advisory board meetings where you made presentations on the target capture patents?

A. Yes.

Q. Was he also on the partnership committee?

A. Yes.

Q. Was Dr. Orgell on the partnership committee?

A. No, not that I remember.

Q. Now, a cc apparently of this letter, Exhibit 131, also apparently went to Mr. Carpenter?

A. Yes.

Q. I think you've already said that he was the president of Gene-Trak and worked at Integrated Genetics and then Gensyme?

A. Yes.

Q. At some point in time Integrated Genetics merged with Gensyme; is that right?

A. Yes.

Q. When you wrote letters to Dr. Orgell and sent copies to Mr. Connoy and Dr. Royer and Mr. Carpenter, did you try to be accurate?

A. I tried to be accurate, yes.

Q. I'd like you to look at Page 1 of the letter. You had a chance, when you went with Mr. Banks, to read your description here on Pages 1 and 2 of Technology Asset No. 1?

A. Yes.

Q. And after reading that, did you have the understanding that what's set forth here is a discussion of the subject matter of the '338 patent?

MR. BANKS: Object to form.

A. I only knew this then as however I reference -- I don't know. It's just something

of that ever change your understanding about what the patent covered?

A. I'm sorry.

Q. That was a terrible question, wasn't it.

A. I don't understand.

Q. Whether you were right or wrong, the letter sets forth your impression at the time of what technology was covered by a patent application that was pending?

MR. BANKS: Object to form.

A. I will repeat this again. I assumed this was the same stuff John had talked to me about years before. I didn't want to see it drop. It's that simple. There isn't any more or less to it.

Q. The letter does, though, set forth your understanding of what the technology was?

A. Yes, as I understood it, and as I could relay it.

Q. Did your understanding ever change after you wrote the letter?

A. No, I don't think so.

Q. Did anybody who got a copy of the

letter call you or write you and tell you you had inaccurately described the technology?

A. I don't remember. I don't remember. I don't even know if they read it.

Q. But you don't remember anybody calling you --

A. I don't remember that.

Q. I'm sorry, I've got to get the whole question out.

You don't remember anybody calling you and telling you you had incorrectly described the technology?

A. I don't remember.

Q. As you sit here today, do you have any reason to believe that you misunderstood the technology covered by the pending patent application?

A. No. I think it's -- what I've read, no.

Q. Do you know why there's no reference in the patent to PCR type amplification?

A. No. I didn't write it.

Q. Now, in 1986/1987, a scientist who was going to use nonspecific amplification would

come from Tony. But this stuff on and on, you go on. Temperature required, another approach would be to transcriptase. All of this was free form text writing. I was trying to sell Carl Orgell to pick this thing up. I didn't want to get too technical, or he would put it down, which is probably what everybody did anyway.

Q. You wanted to be accurate in describing --

A. Tried to be as accurate as possible.

Q. We've talked about Tony here in our recent conversations. Tony was Tony Janiuk?

A. Yes.

Q. And he was Gene-Trak's patent counsel?

A. He sat across the way.

Q. Yes, he was Gene-Trak's patent counsel?

A. Yes.

Q. And you had discussions with him about the CIP application?

A. Yes, clearly.

Q. In 1989, did you have any understanding at all of the term "reduction to practice"?

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC., Defendant.	No. 99cv2668 H (AJB) **NOTICE OF LODGMENT IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT** Date: May 29, 2001 Time: 10:30 a.m. Dept: Courtroom 1

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE that Plaintiff Gen-Probe Incorporated hereby lodges the following exhibits in support of Gen-Probe Incorporated's Motion for Partial Summary Judgment:

EXHIBIT 1: A true and correct copy of a letter dated December 15, 1989 from Dr. Richards to Dr. Orgell

EXHIBIT 2: "Base" Illustration

EXHIBIT 3: "Double Helix" Illustration

EXHIBIT 4: "Complementary Base Pair" Illustration

EXHIBIT 5: "Probe" Illustration

EXHIBIT 6: "Target Capture" Illustration

EXHIBIT 7: "Specific Primer" Illustration

EXHIBIT 8: United States Patent No. 5,750,338, entitled "Target and Background Capture Methods with Amplification For Affinity Assays," issued May 12, 1998, to Mark L. Collins et al.

EXHIBIT 9: True and correct copies of excerpts of the transcript of the deposition of Jonathan Lawrie, Ph.D. taken February 15, 2001 **(FILED UNDER SEAL)**

EXHIBIT 10: True and correct copies of excerpts of the transcript of the deposition of James Richards, Ph.D. taken March 30, 2001 **(FILED UNDER SEAL)**

Dated: April 30, 2001

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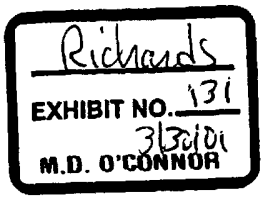
December 15, 1989



Dear Dr. Orgell:

Pat Connoy has asked me to write to you to outline potential valuable assets which are owned entirely by either Amoco or GENE-TRAK and which require a modest outside research effort to demonstrate technical feasibility and possibly product concept feasibility. In all three cases, patent applications have been prepared and filed which either cover the method or process. Originally, I had intended to present these concepts to the Biotechnology group (Ken Cruickshank et al.) during a scheduled visit on December 12, 1989, but this visit was canceled by Amoco.

Technology Asset #1-Target and background capture methods with amplification for affinity assays (USSN 922,155). This application relates to the so-called "Collins Application" which is background reduction in a nucleic acid hybridization assay. The primary patent was prepared and filed by A.J. Janiuk on October 23, 1989. A CIP to this application was filed about a year later which included inventive material relating to target amplification following target capture and was conceived at Amoco by King, Halbert and Lawrie. In essence, one round of target capture and release results in a highly enriched population of target DNA molecules compared to non-target or background DNA molecules. Random hexanucleotides are then allowed to anneal to multiple sites along the length of all DNA molecules contained in the target DNA-enriched sample. All primer-template complexes become substrates for the Klenow fragment of DNA polymerase I. The enzyme synthesizes new DNA by incorporating nucleoside monophosphates at the free 3'-OH group provided by the primer. The newly synthesized DNA can serve as template for subsequent cycles of such an amplification process. One can envision using the Stratagene Cloning System i.e., Prime-It™ Random Primer Kit which uses T7 pol and random primers to achieve the same goal much faster. Obviously, in both cases, temperature cycling would be required to obtain multiple copies. Another approach would be to use a transcriptase capable of initiating from a random promoter or primer and thus giving rise to 10->100->1000 RNA copies per recognized DNA template.

131

The important concept in this invention is that without target enrichment one would amplify noise or background polynucleotides in proportion to target polynucleotides and thereby gain nothing. Cetus, Sibia/Salk, Biotechnica, etc. all claim **specific** primers for amplification whereas the present invention claims use of the opposite, namely, **non-specific** primers or promoters. Consequently, target enrichment becomes the enabling aspect of the amplification method. In practice, one would hybridize targets with a specific poly(A)-tailed capture probe, retrieve hybrid complexes by binding to oligo (dT) support and wash away non-hybridized polynucleotides. Following extensive washing, captured target polynucleotides could be released and the non-specific amplification process could take place. After amplification (10-100X) the polynucleotide containing solution could be subjected to 2-3 rounds of target capture and release using A-tailed capture probes and MDV-1 label probe and finally detected using the Qß replicase real time fluorescent detection system. I believe such an approach could have significant value in the area of blood bank screening or any application where there is a very critical need for exquisite sensitivity e.g., <10 molecules/specimen. GENE-TRAK is confident that we can achieve 500-1000 molecule sensitivity with target cycling and Qß-smart probes but we will always be limited by the amount of original target polynucleotide present in the sample.

I would add that this application would also eliminate possible GenProbe patent problems since we could target DNA rather than ribosomal RNA. Obviously there are many questions which must be addressed but I feel that a successful reduction to practice of this invention would have great value for GENE-TRAK and Amoco. -Furthermore, since the patent application was filed by Amoco, a successful reduction to practice properly falls within the scope of Amoco Biotechnology research and development.

REDACTED

We are interested in reviewing these projects with Amoco biotechnology at your earliest convenience. GENE-TRAK was planning to allocate resources to these projects but our 1990 budget has made that very difficult. If Amoco is unable to allocate resources, GENE-TRAK will actively seek outside funding or co-development partners were appropriate. I would appreciate your consideration of these matters and comments, and as mentioned at the beginning of this letter, I would be pleased to present these concepts to you and your staff. Finally, I look forward to meeting you in the future.

Thank you in advance for your consideration of this information and on behalf of GENE-TRAK Systems I wish you and your organization the very best of Holiday greetings and a Happy (and successful) New Year!

Sincerely,

James C. Richards
Director,
Business Development & Licensing

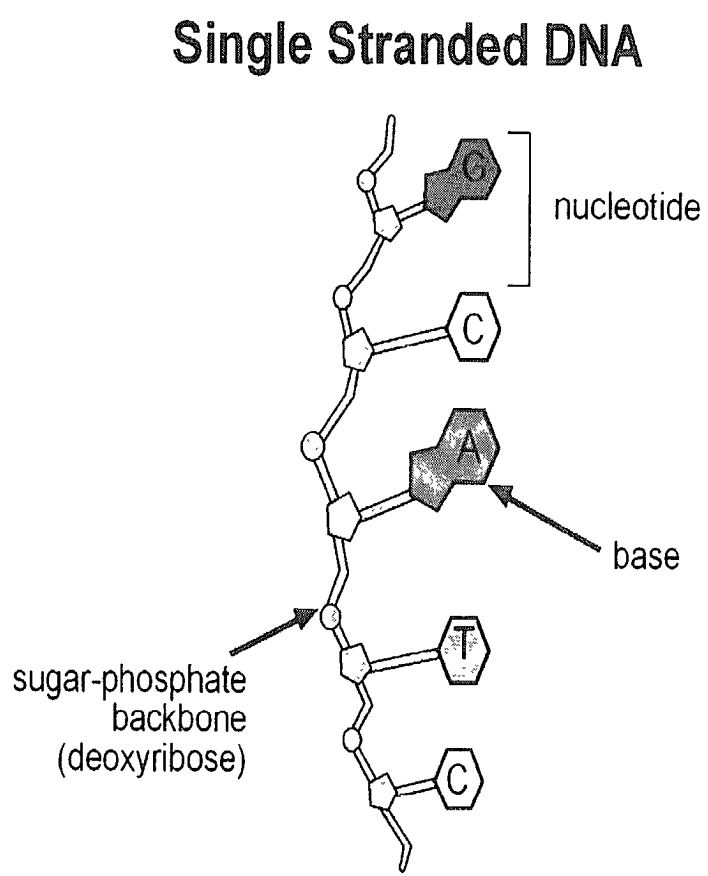
cc
Patrick J. Connoy, GENE-TRAK Systems
Bruce Neri, GENE-TRAK Systems
G.P. Royer, Amoco Technology
J. Triebe, Amoco Technology
E. Jones, Amoco Technology
R. Carpenter, Genzyme Corp.
file

DNA STRUCTURE

Four bases: "G", "C", "A", "T"

Sugar-phosphate backbone, where the sugar is deoxyribose.

Base + sugar-phosphate backbone = "NUCLEOTIDE"



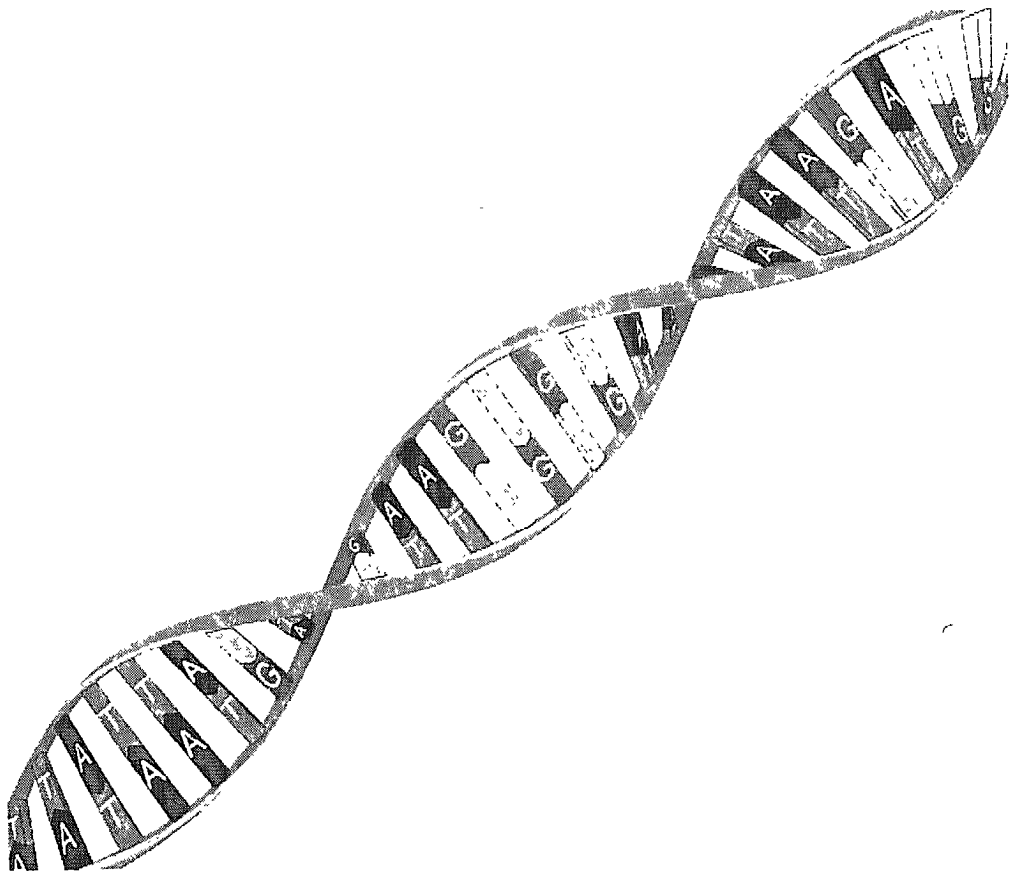
Ex. 2 Pg. 8

EXHIBIT 3

DNA DOUBLE HELIX

- The helix stabilizes the complementary DNA strands and helps to hold them together
- The helix is most stable when the bases are properly paired
- The two strands can be separated by heating the DNA

The Double Helix

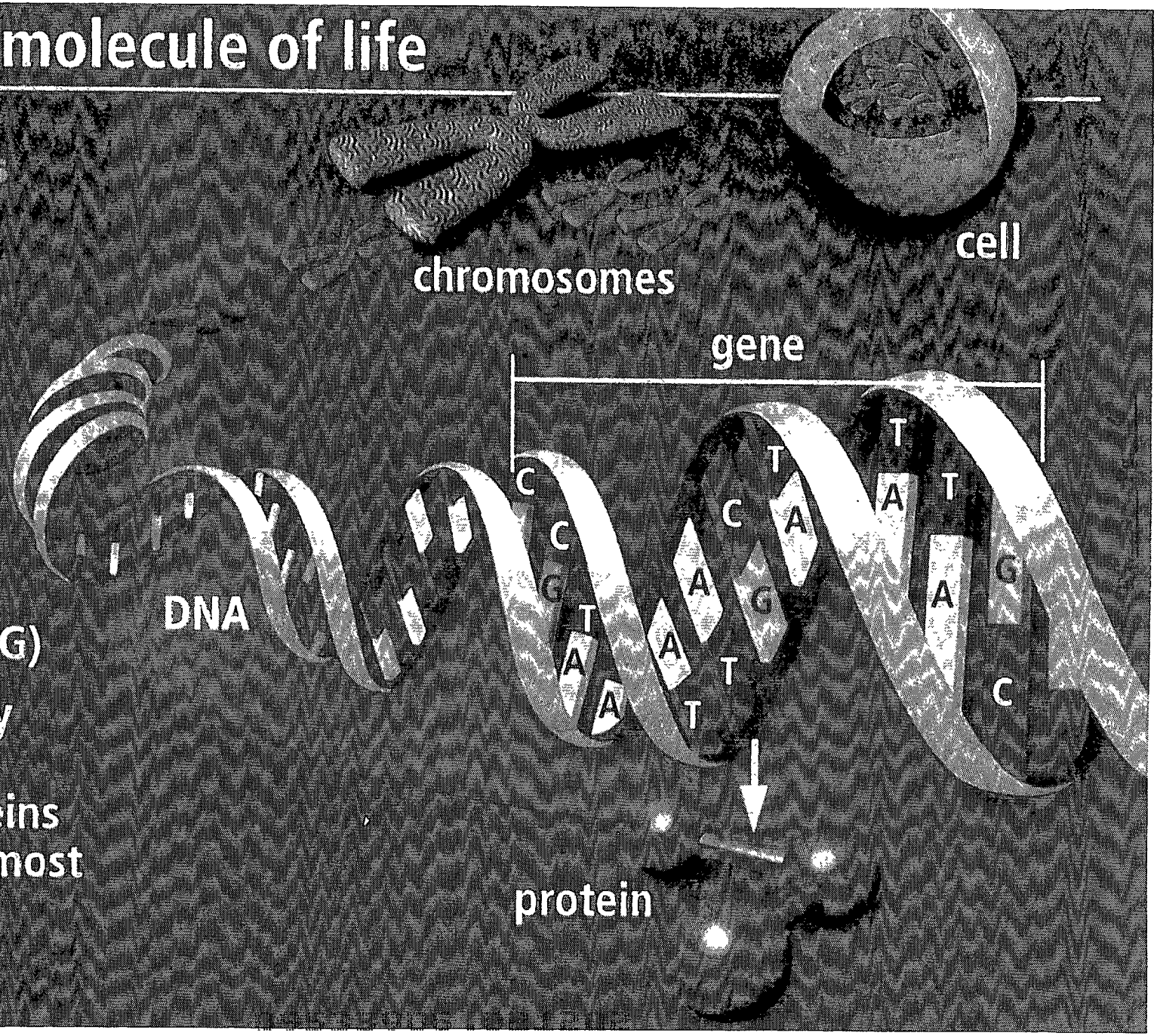


DNA the molecule of life

Trillions of cells

Each cell:

- 46 human chromosomes
- 2 meters of DNA
- 3 billion DNA subunits (the bases: A, T, C, G)
- Approximately 30,000 genes code for proteins that perform most life functions

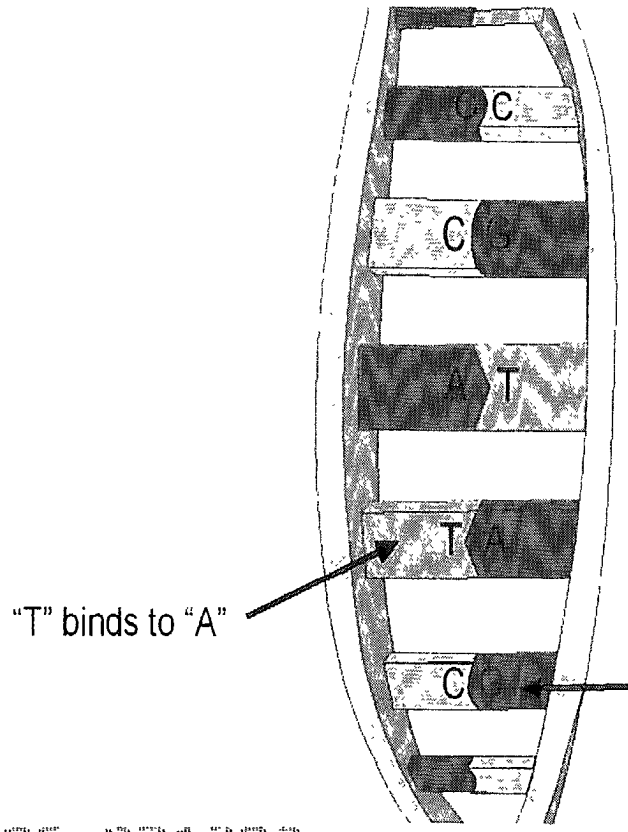


COMPLEMENTARY BASE PAIRING

- Two strands of DNA that have 'matching' sequences, are COMPLEMENTARY.
- That is ...

STRAND 1		STRAND 2
G	binds with	C
C	binds with	G
A	binds with	T
T	binds with	A

Complementary Base Pairing

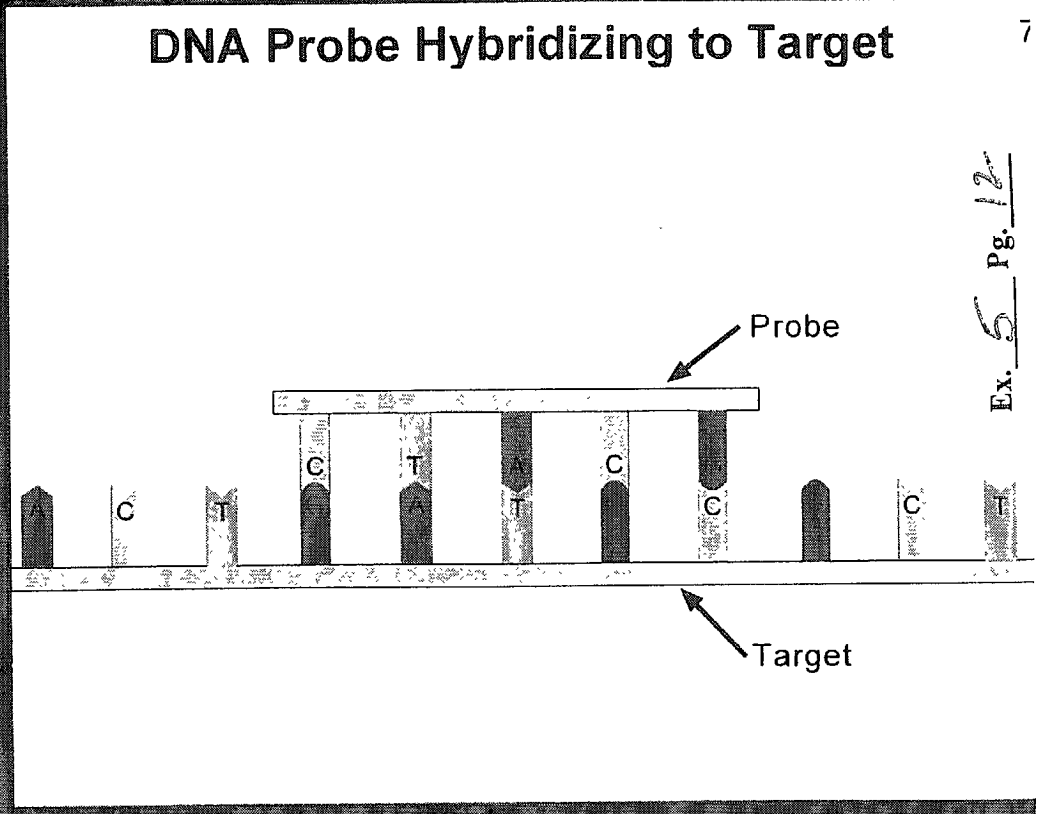


Ex. 4 Pg. 11

3906.021202

PROBES

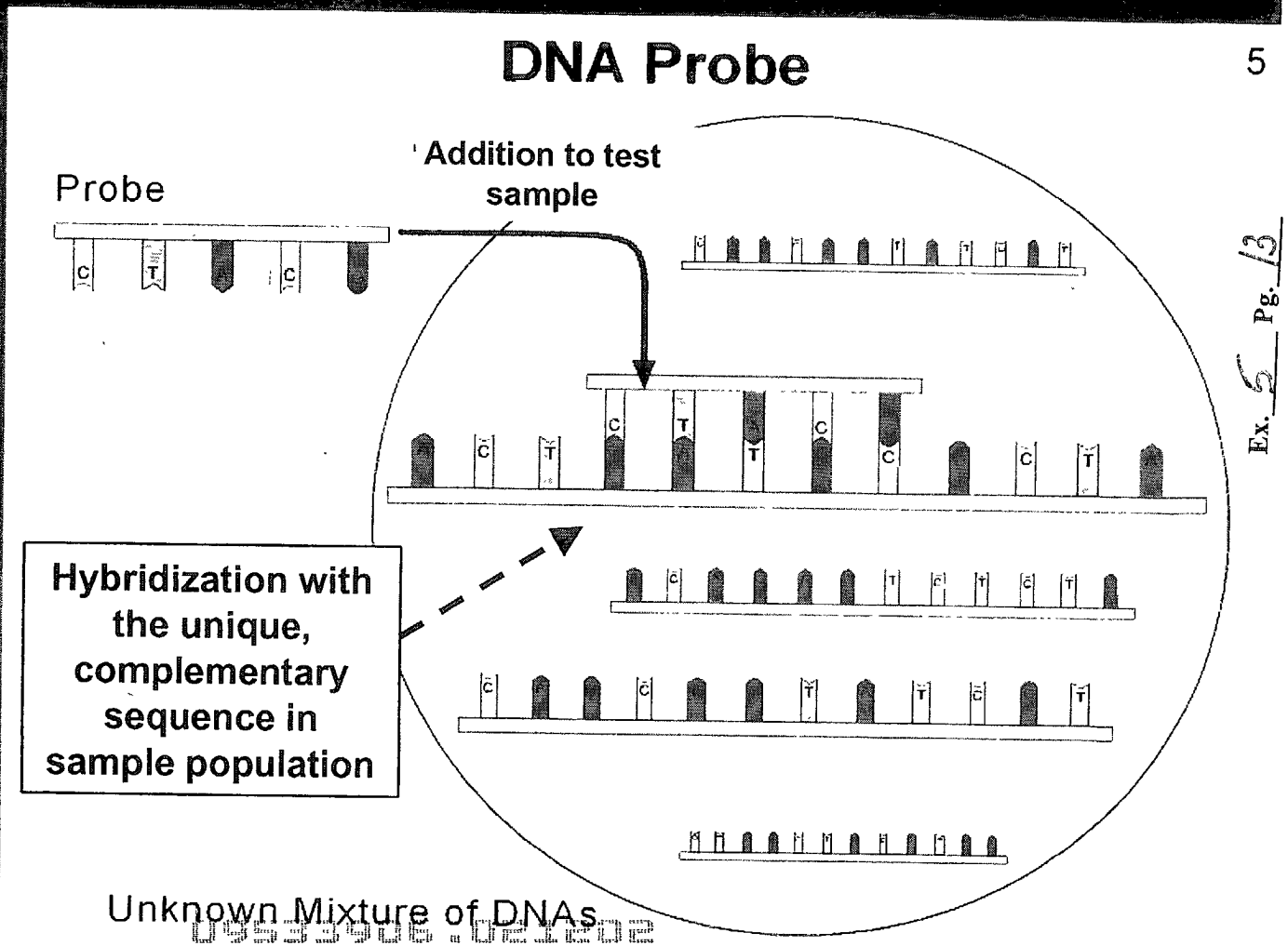
- Complementarity nature of nucleotides exploited for use in diagnostics.
- Single stranded DNA of a target population (*e.g.*, bacteria) will bind with the single-stranded DNA probe IF the sequences are complementary to one another.



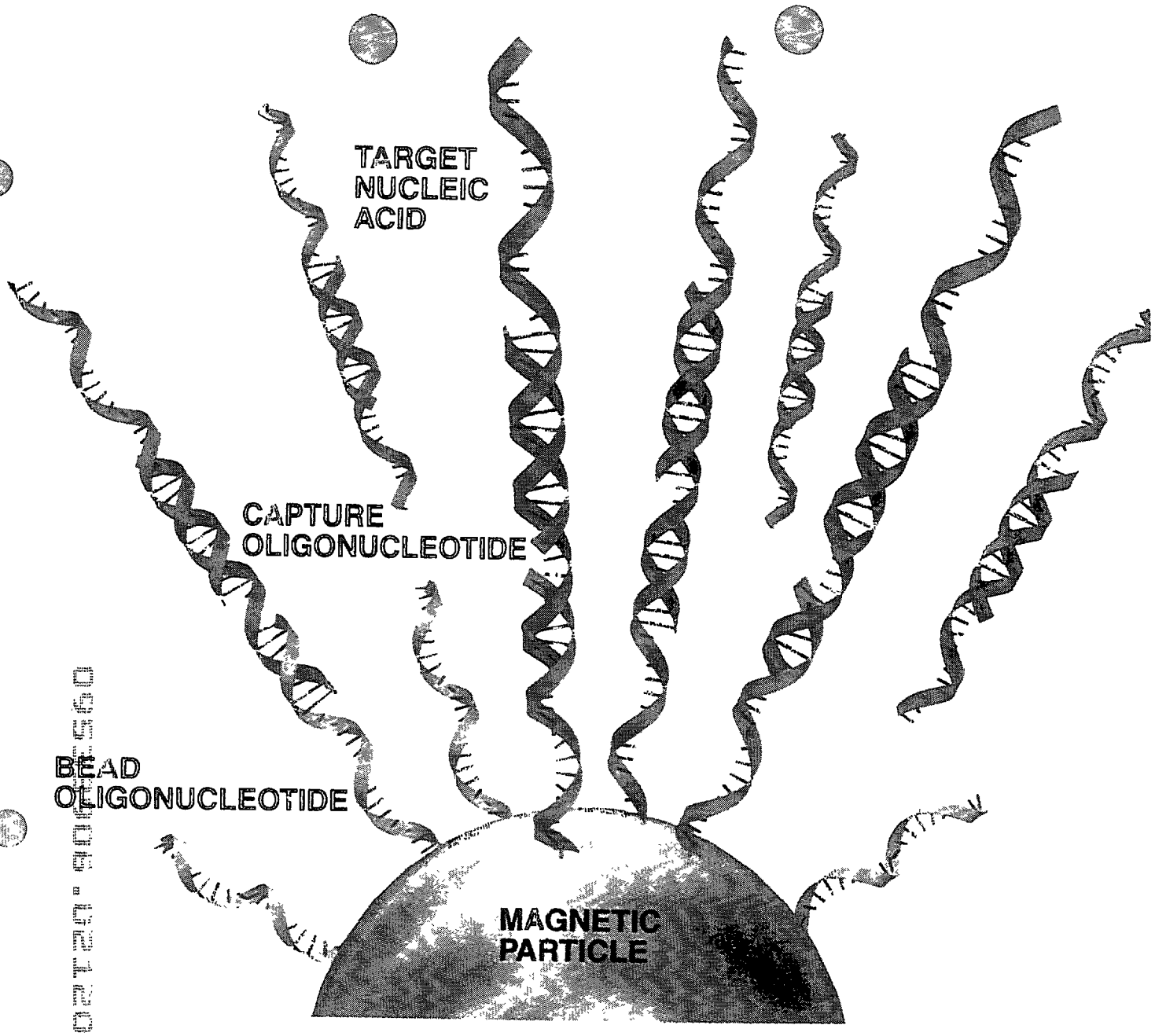
Ex. 5 Pg. 12

PROBES, *cont.*

- DNA hybridizes to target.
- Does not hybridize to other DNA sequences.



Ex. 5 Pg. 13



Page 5 of 6

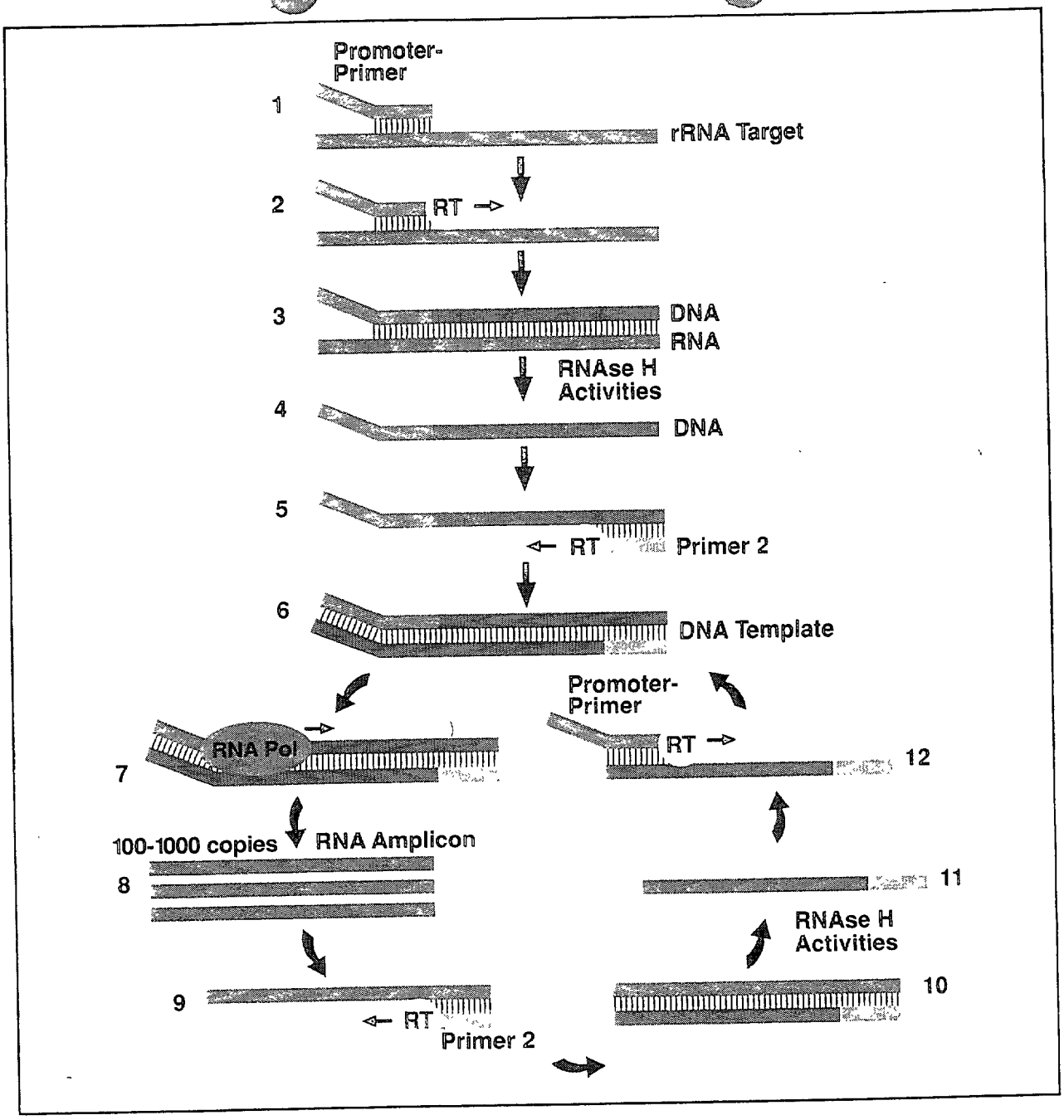


FIGURE 1. Transcription-Mediated Amplification Cycle (TMA):

Step 1: Promoter-primer binds to rRNA target.

Step 2: Reverse Transcriptase (RT) creates DNA copy of rRNA target.

Step 3: RNA:DNA duplex.

Step 4: RNAse H activities of RT degrades the rRNA.

Step 5: Primer 2 binds to the DNA and RT creates a new DNA copy.

Step 6: Double-stranded DNA template with a promoter sequence.

Step 7: RNA polymerase (RNA Pol) initiates transcription of RNA from DNA template.

Step 8: 100-1000 copies of RNA amplicon are produced.

Step 9: Primer 2 binds to each RNA amplicon and RT creates a DNA copy.

Step 10: RNA:DNA duplex.

Step 11: RNAse H activities of RT degrades the rRNA.

Step 12: Promoter-primer binds to the newly synthesized DNA. RT creates a double-stranded DNA and the autocatalytic cycle repeats resulting in a billion-fold amplification.

US005750338A

United States Patent [19]

Collins et al.

[11] Patent Number: 5,750,338

[45] Date of Patent: May 12, 1998

[54] **TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS**

[75] Inventors: **Mark L. Collins**, Holden; **Donald N. Halbert**, Milford; **Walter King**, Maynard; **Jonathan M. Lawrie**, Milford, all of Mass.

[73] Assignee: **Amoco Corporation**, Chicago, Ill.

[21] Appl. No.: **238,080**

[22] Filed: **May 3, 1994**

Related U.S. Application Data

[62] Division of Ser. No. 400,657, Mar. 8, 1995, which is a continuation of Ser. No. 257,469, Jun. 8, 1994, abandoned, which is a continuation of Ser. No. 124,826, Sep. 21, 1993, abandoned, which is a continuation of Ser. No. 946,749, Sep. 17, 1992, abandoned, which is a continuation of Ser. No. 648,468, Jan. 31, 1991, abandoned, which is a continuation-in-part of Ser. No. 922,155, Oct. 23, 1986, abandoned, and Ser. No. 136,920, Dec. 21, 1987, abandoned.

[51] Int. Cl.[6] C07H 21/04; C12Q 1/68; C12Q 1/70; C12P 19/34

[52] U.S. Cl. 435/6; 435/5; 435/91.2; 435/174; 435/7.1; 536/24.3; 536/24.32; 536/24.33

[58] Field of Search 435/6, 5, 91.2, 435/174, 7.1, 7.9; 536/24.3-24.33, 26.6

[56] **References Cited**

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5,200,314	4/1993	Urdea et al.	435/6
5,232,829	8/1993	Longiaru et al.	435/6

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0 139 489	5/1985	European Pat. Off. .
0 159 719	10/1985	European Pat. Off. .

Primary Examiner—W. Gary Jones
Assistant Examiner—Dianne Rees
Attorney, Agent, or Firm—Norval B. Galloway

[57] **ABSTRACT**

A method of assay for target polynucleotides includes steps of isolating target polynucleotides from extraneous non-target polynucleotides, debris, and impurities and amplifying the target polynucleotide.

40 Claims, 10 Drawing Sheets

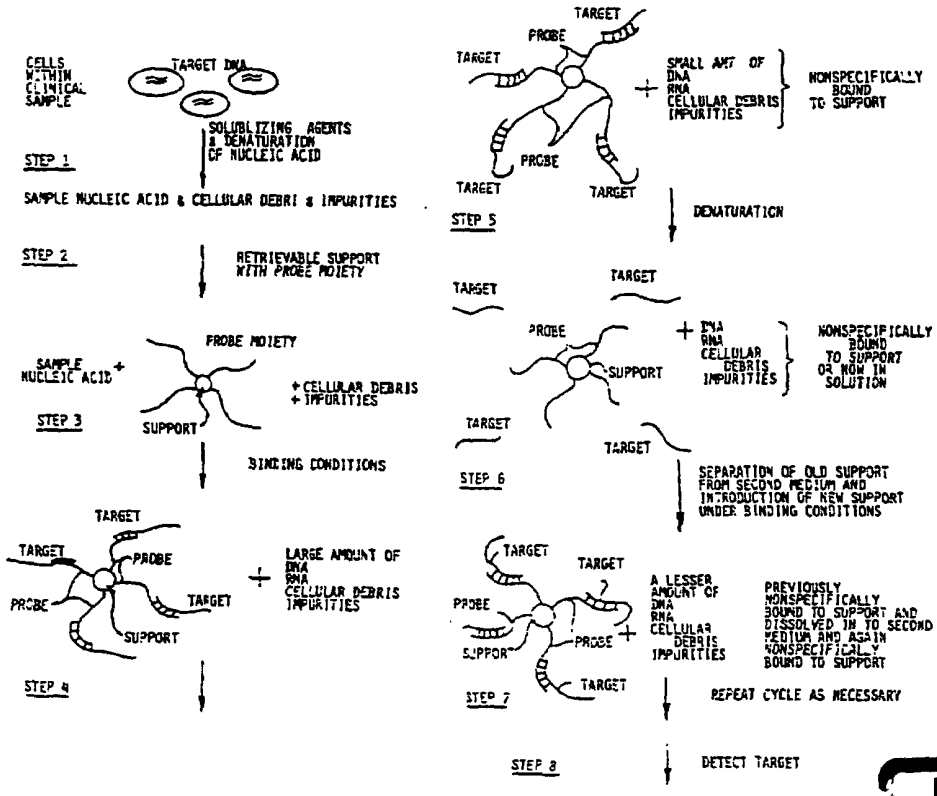


FIG. 1a

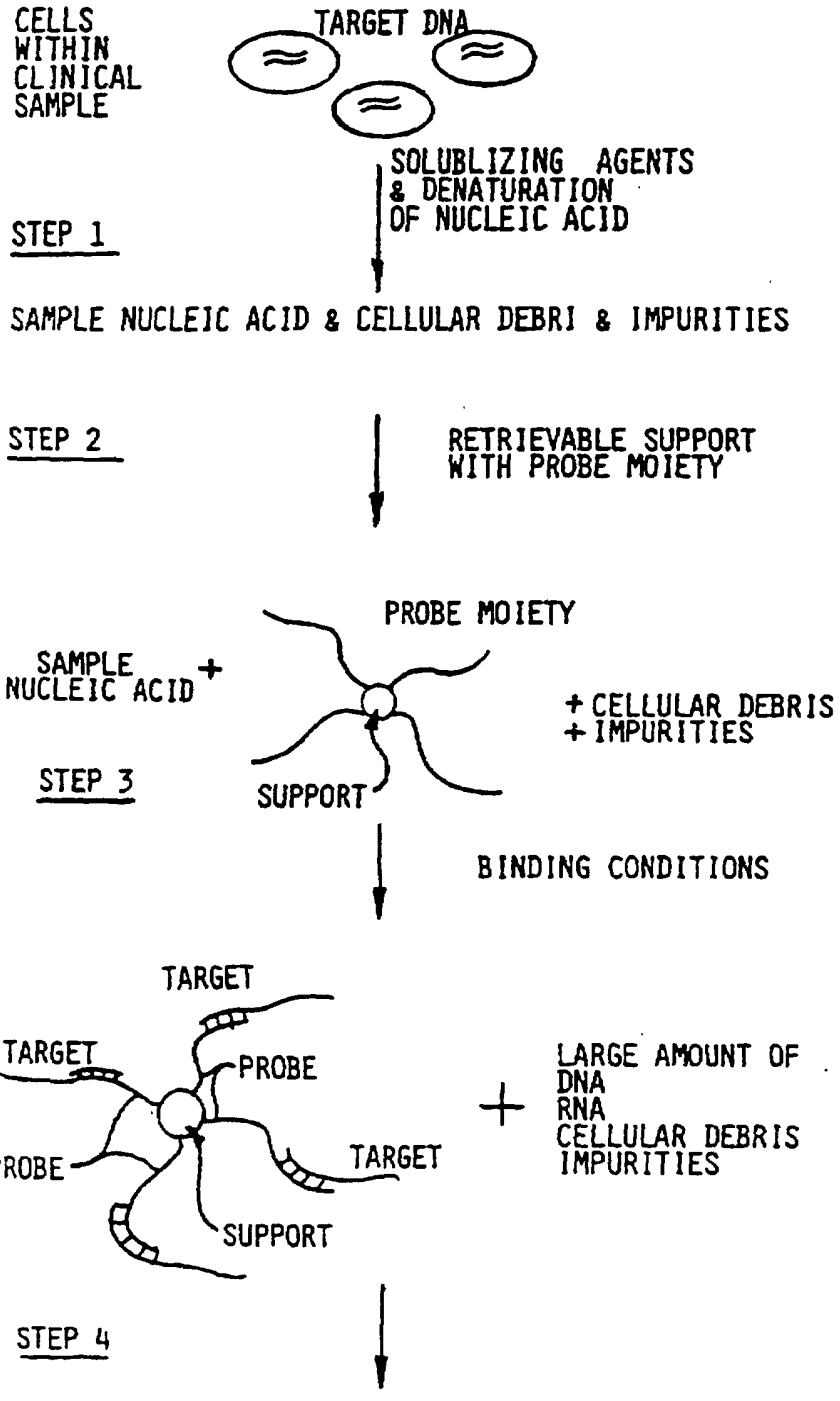

CELLS WITHIN CLINICAL SAMPLE
TARGET DNA
SOLUBLIZING AGENTS & DENATURATION OF NUCLEIC ACID
STEP 1
SAMPLE NUCLEIC ACID & CELLULAR DEBRI & IMPURITIES
STEP 2
RETRIEVABLE SUPPORT WITH PROBE MOIETY
PROBE MOIETY
SAMPLE NUCLEIC ACID +
+ CELLULAR DEBRIS
+ IMPURITIES
STEP 3
SUPPORT
BINDING CONDITIONS
TARGET
TARGET
PROBE
PROBE
TARGET
SUPPORT
+
LARGE AMOUNT OF DNA
RNA
CELLULAR DEBRIS
IMPURITIES
STEP 4

FIG. 1b

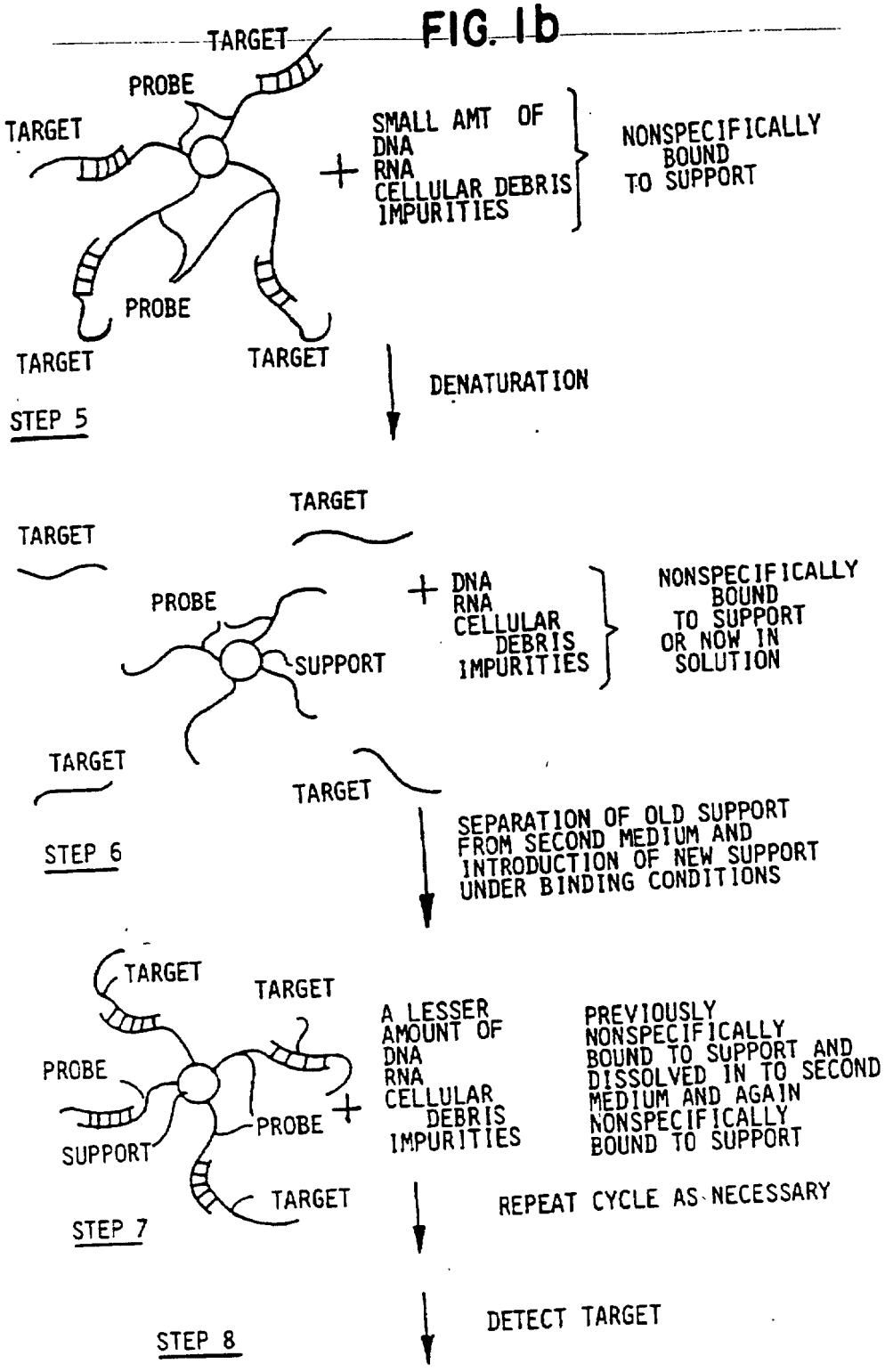

TARGET
PROBE
TARGET
SMALL AMT OF DNA RNA CELLULAR DEBRIS IMPURITIES
NONSPECIFICALLY BOUND TO SUPPORT
PROBE
TARGET
TARGET
DENATURATION
STEP 5
TARGET
TARGET
PROBE
SUPPORT
DNA RNA CELLULAR DEBRIS IMPURITIES
NONSPECIFICALLY BOUND TO SUPPORT OR NOW IN SOLUTION
TARGET
TARGET
STEP 6
SEPARATION OF OLD SUPPORT FROM SECOND MEDIUM AND INTRODUCTION OF NEW SUPPORT UNDER BINDING CONDITIONS
TARGET
TARGET
PROBE
PROBE
SUPPORT
TARGET
A LESSER AMOUNT OF DNA RNA CELLULAR DEBRIS IMPURITIES
PREVIOUSLY NONSPECIFICALLY BOUND TO SUPPORT AND DISSOLVED IN TO SECOND MEDIUM AND AGAIN NONSPECIFICALLY BOUND TO SUPPORT
STEP 7
REPEAT CYCLE AS NECESSARY
DETECT TARGET
STEP 8

FIG. 2a

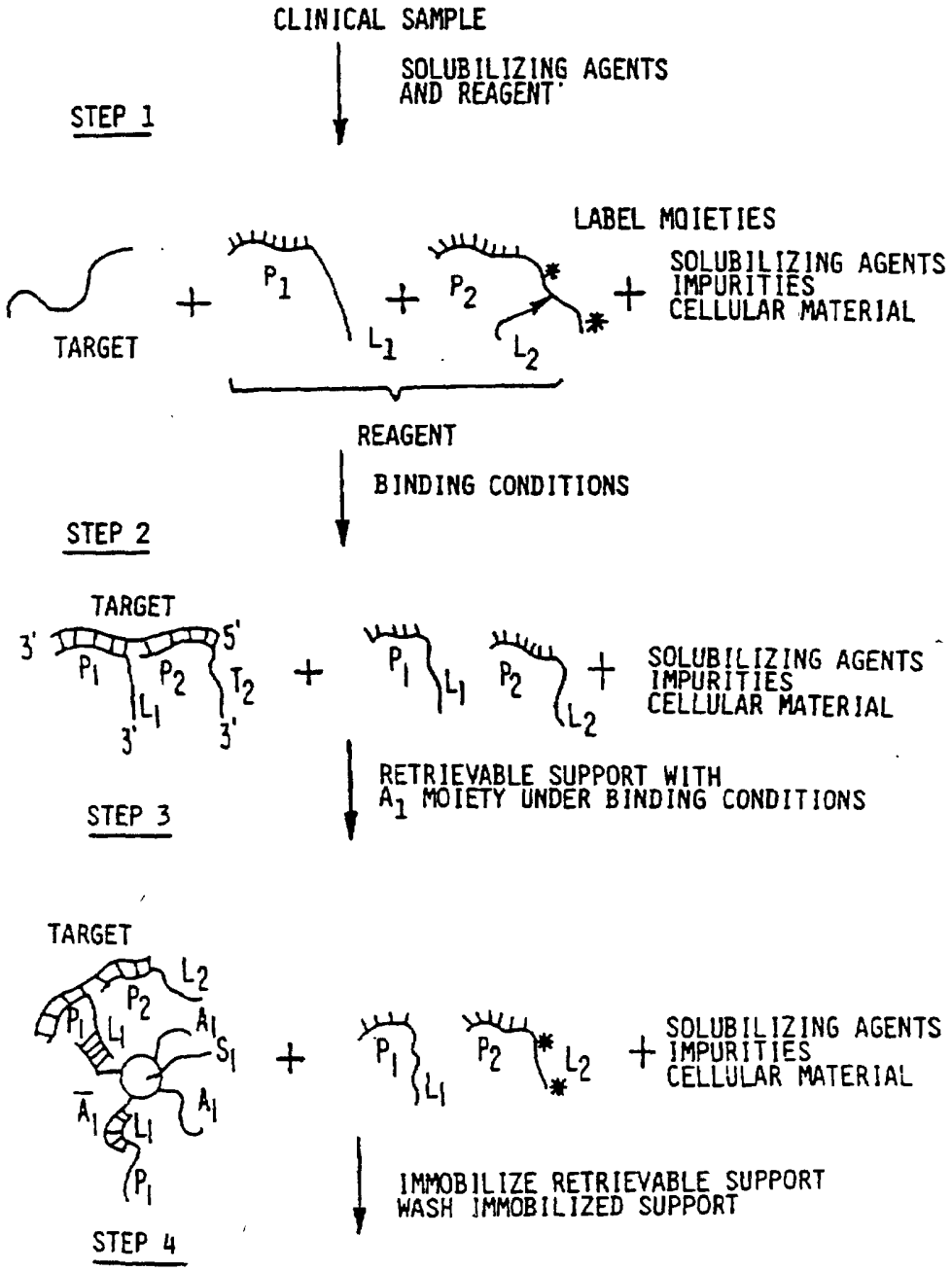

CLINICAL SAMPLE
SOLUBILIZING AGENTS AND REAGENT
STEP 1
LABEL MOIETIES
TARGET
P1
L1
P2
L2
SOLUBILIZING AGENTS IMPURITIES CELLULAR MATERIAL
REAGENT
BINDING CONDITIONS
STEP 2
TARGET
3'
5'
P1
P2
T2
L1
3'
3'
SOLUBILIZING AGENTS IMPURITIES CELLULAR MATERIAL
RETRIEVABLE SUPPORT WITH A1 MOIETY UNDER BINDING CONDITIONS
STEP 3
TARGET
L2
P2
P1
L1
A1
S1
A1
L1
A1
P1
SOLUBILIZING AGENTS IMPURITIES CELLULAR MATERIAL
IMMOBILIZE RETRIEVABLE SUPPORT
WASH IMMOBILIZED SUPPORT
STEP 4

FIG. 2b

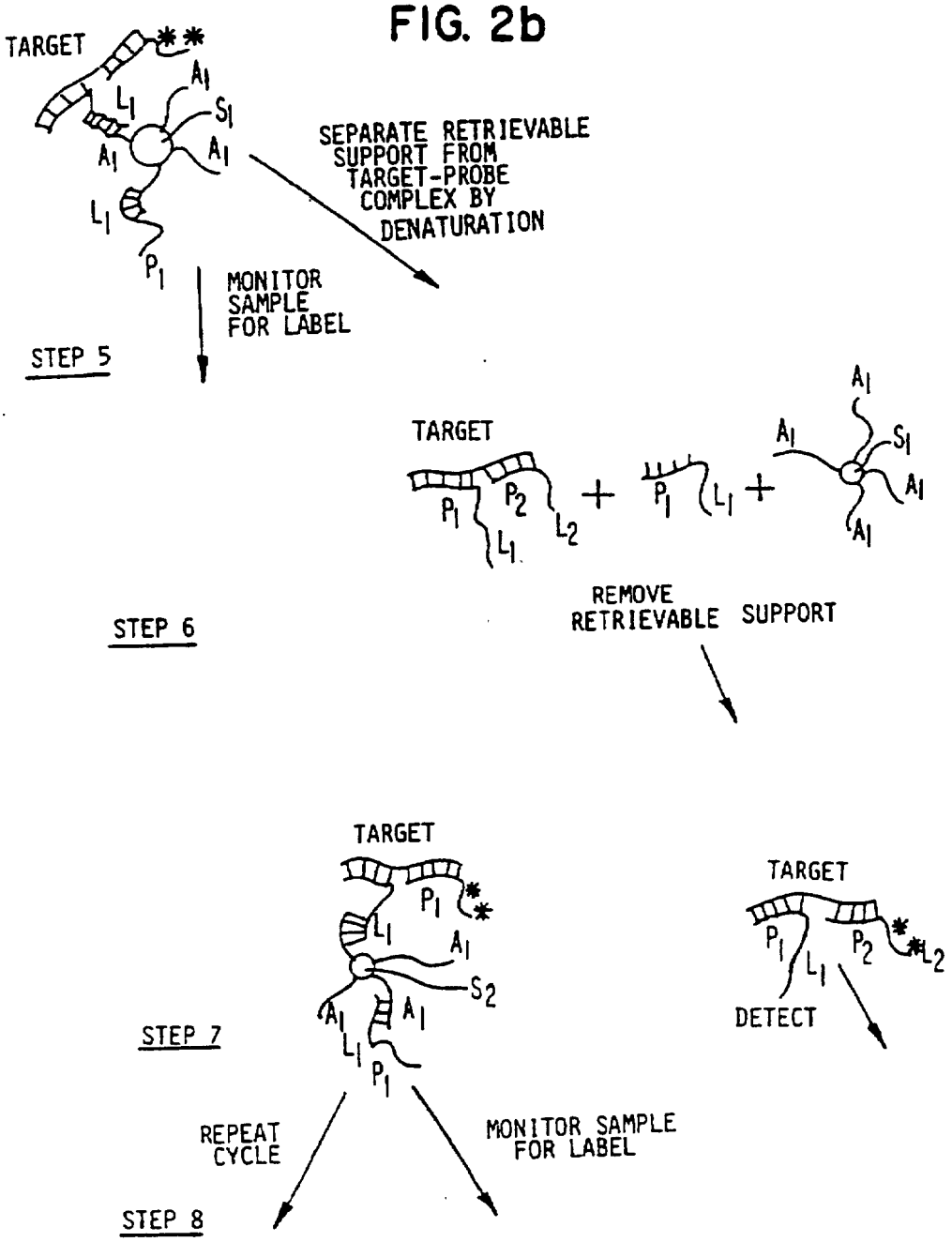

TARGET
A1
L1
S1
A1
A1
L1
P1
SEPARATE RETRIEVABLE SUPPORT FROM TARGET-PROBE COMPLEX BY DENATURATION
MONITOR SAMPLE FOR LABEL
STEP 5
TARGET
P1
P2
L2
L1
P1
L1
A1
S1
A1
A1
REMOVE RETRIEVABLE SUPPORT
STEP 6
TARGET
P1
L1
A1
S2
A1
A1
L1
P1
STEP 7
REPEAT CYCLE
MONITOR SAMPLE FOR LABEL
STEP 8
TARGET
P1
P2
L2
L1
DETECT

FIG. 3

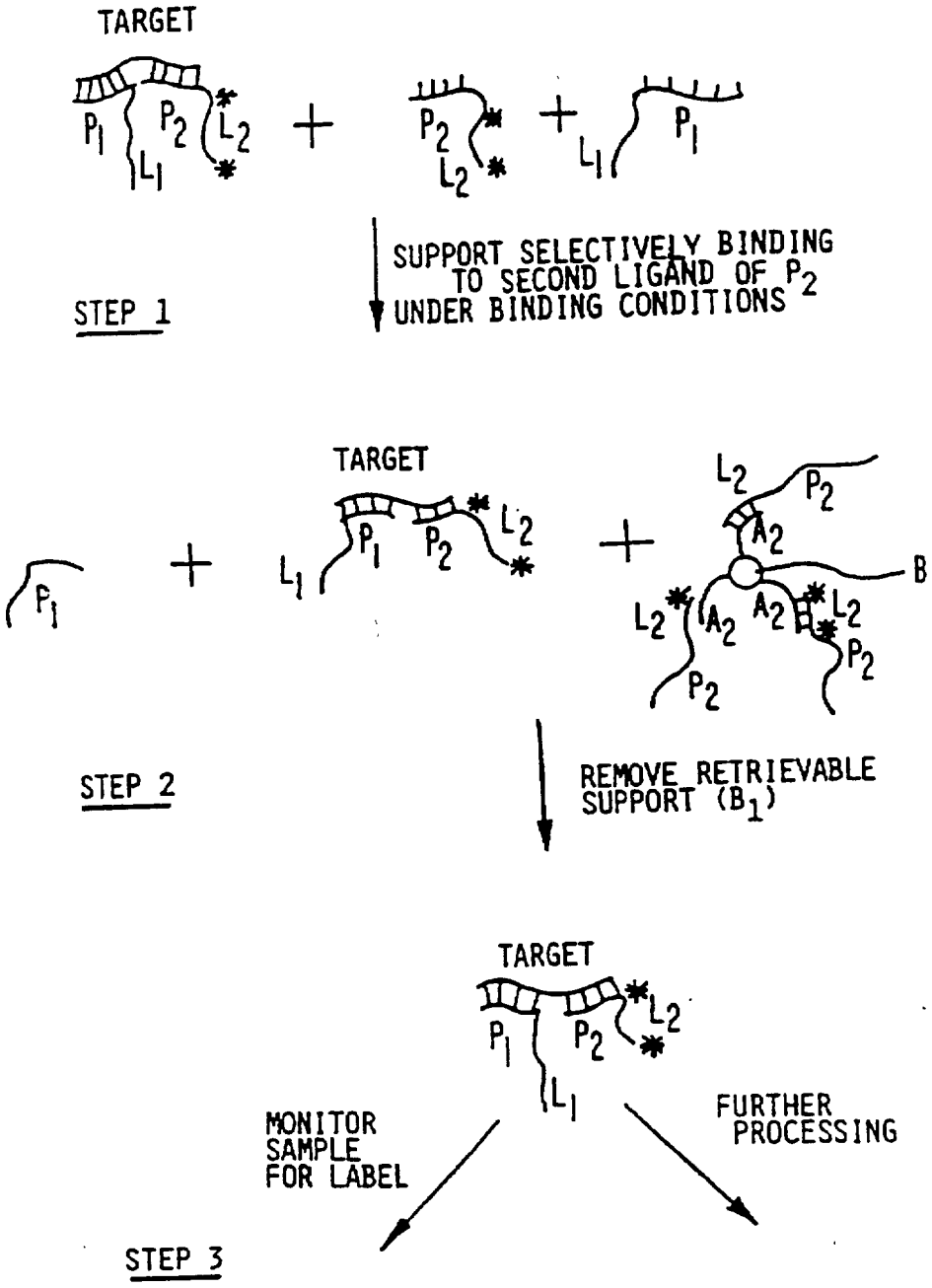


FIG.4

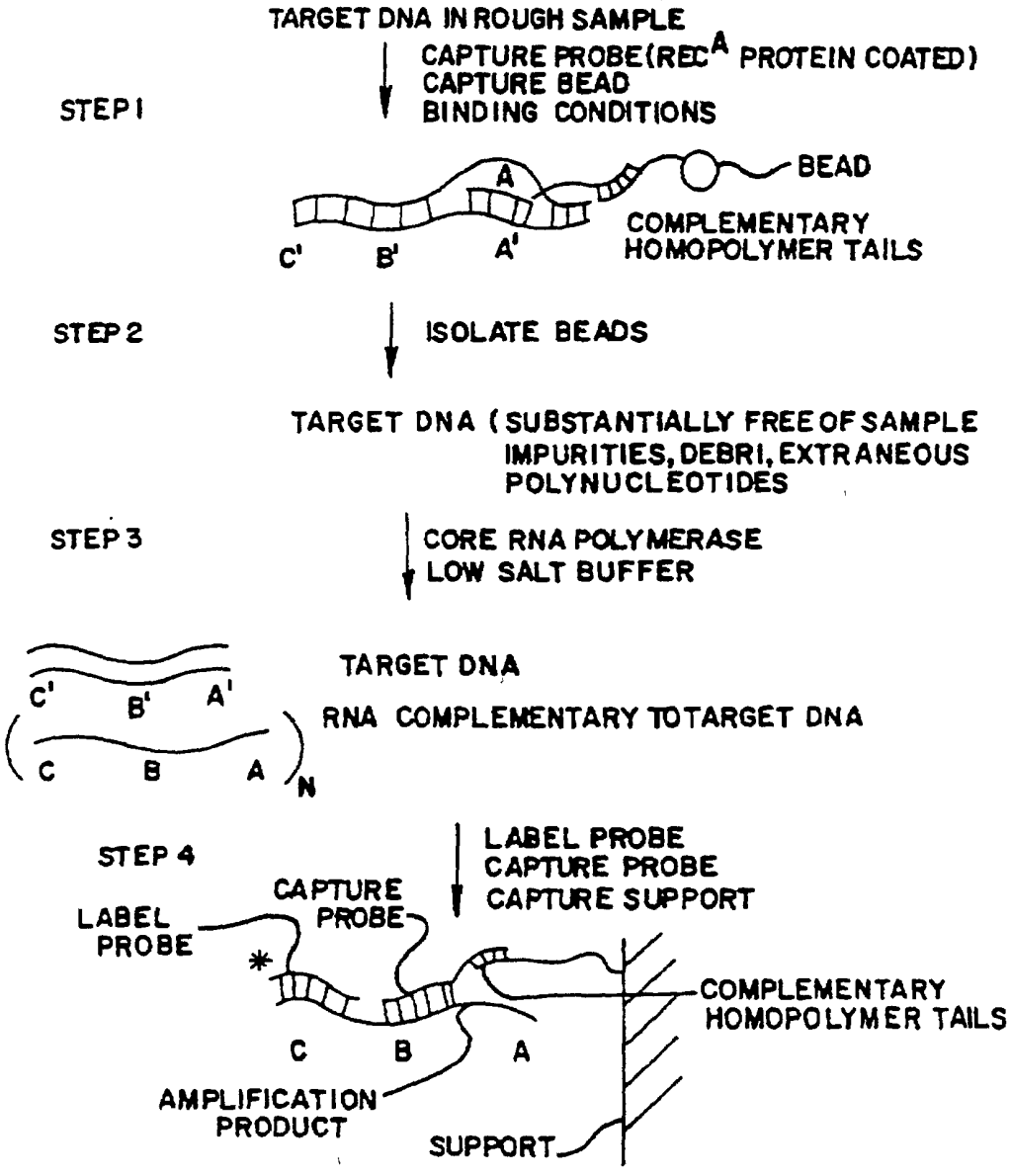

TARGET DNA IN ROUGH SAMPLE
CAPTURE PROBE (REC A PROTEIN COATED)
CAPTURE BEAD
BINDING CONDITIONS
STEP 1
BEAD
A
C' B' A'
COMPLEMENTARY HOMOPOLYMER TAILS
STEP 2
ISOLATE BEADS
TARGET DNA (SUBSTANTIALLY FREE OF SAMPLE IMPURITIES, DEBRI, EXTRANEOUS POLYNUCLEOTIDES
STEP 3
CORE RNA POLYMERASE
LOW SALT BUFFER
TARGET DNA
C' B' A'
C B A N
RNA COMPLEMENTARY TO TARGET DNA
STEP 4
LABEL PROBE
CAPTURE PROBE
CAPTURE SUPPORT
LABEL PROBE
CAPTURE PROBE
*
COMPLEMENTARY HOMOPOLYMER TAILS
C B A
AMPLIFICATION PRODUCT
SUPPORT

FIG. 5

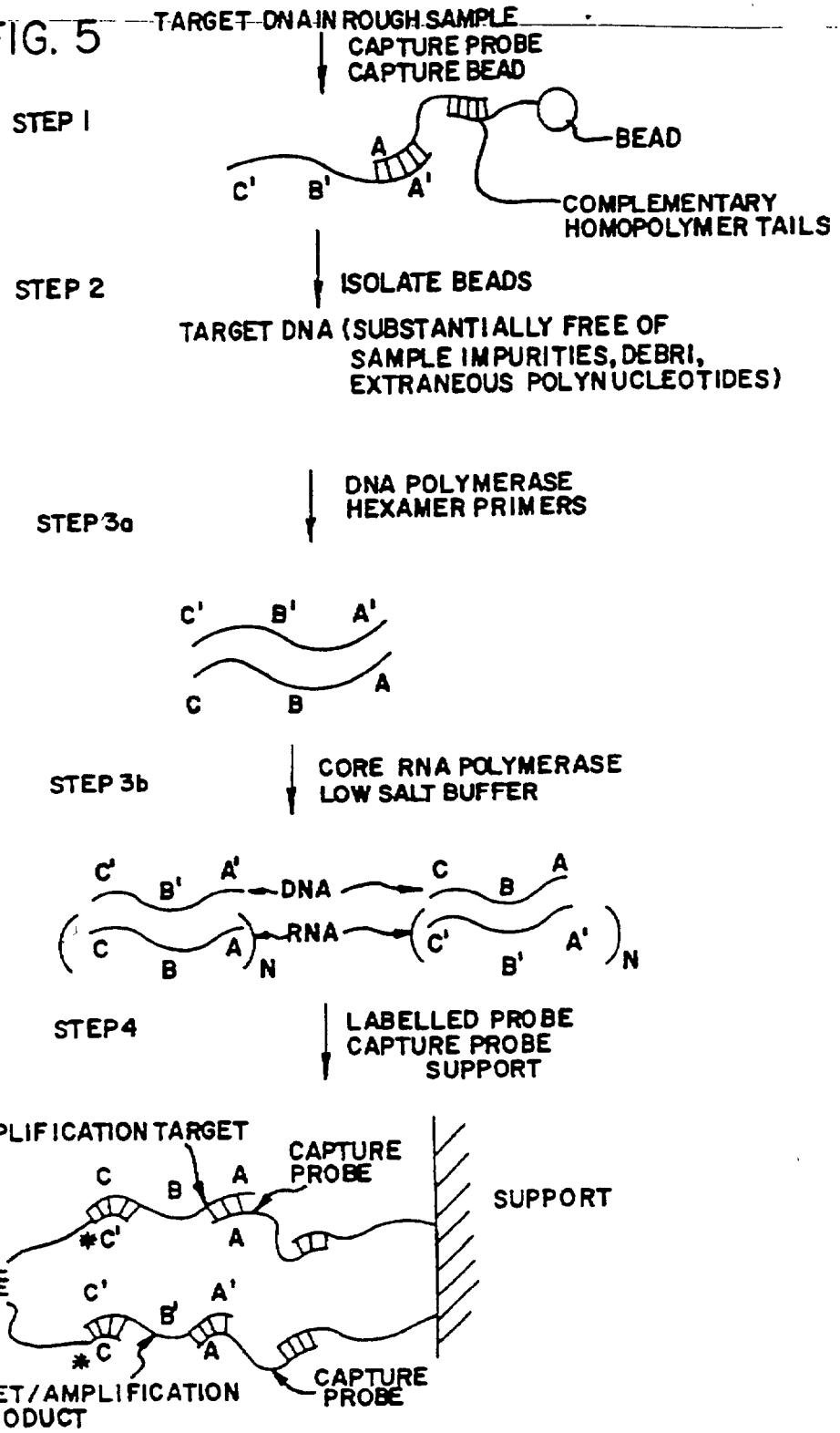
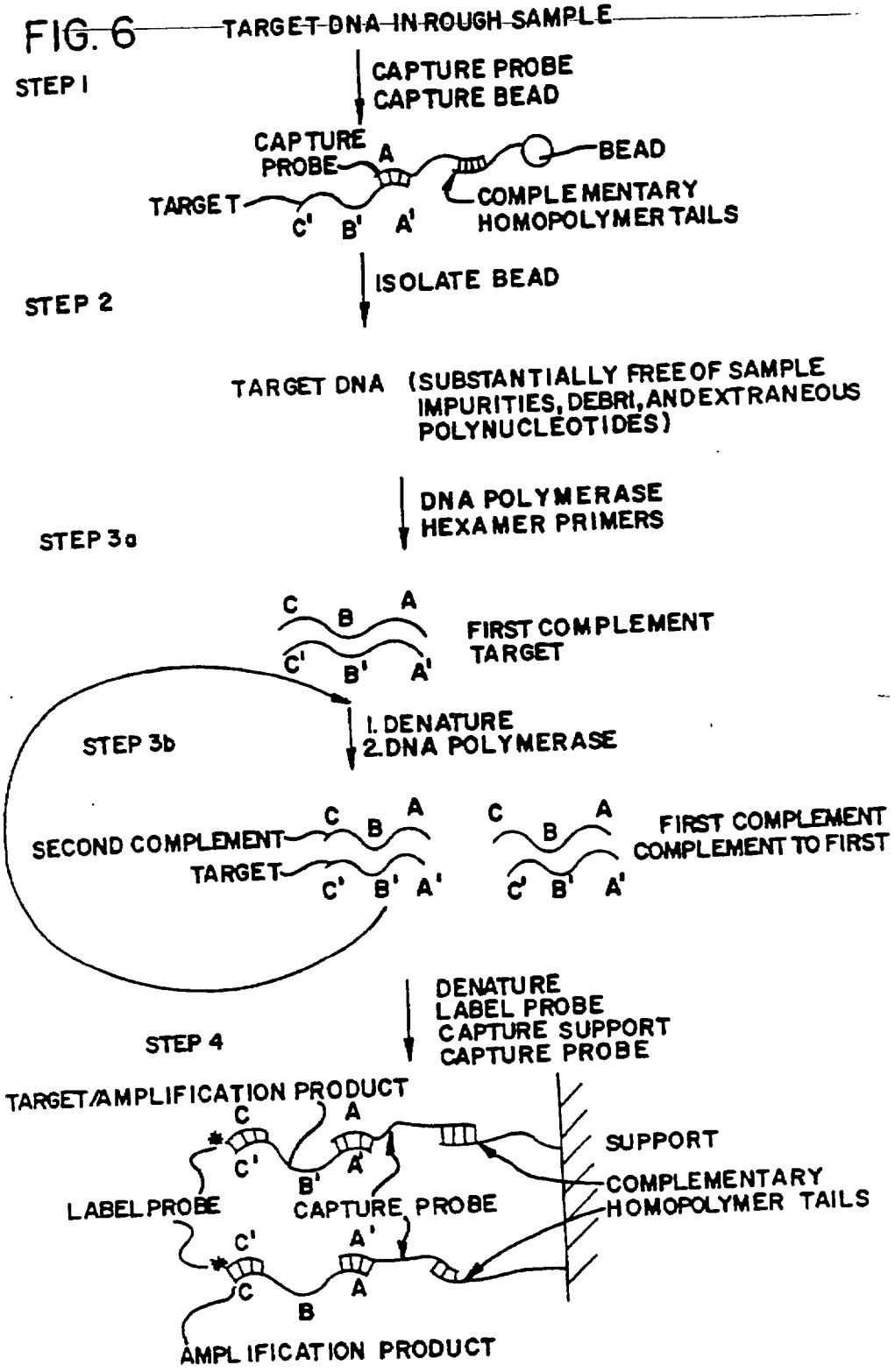
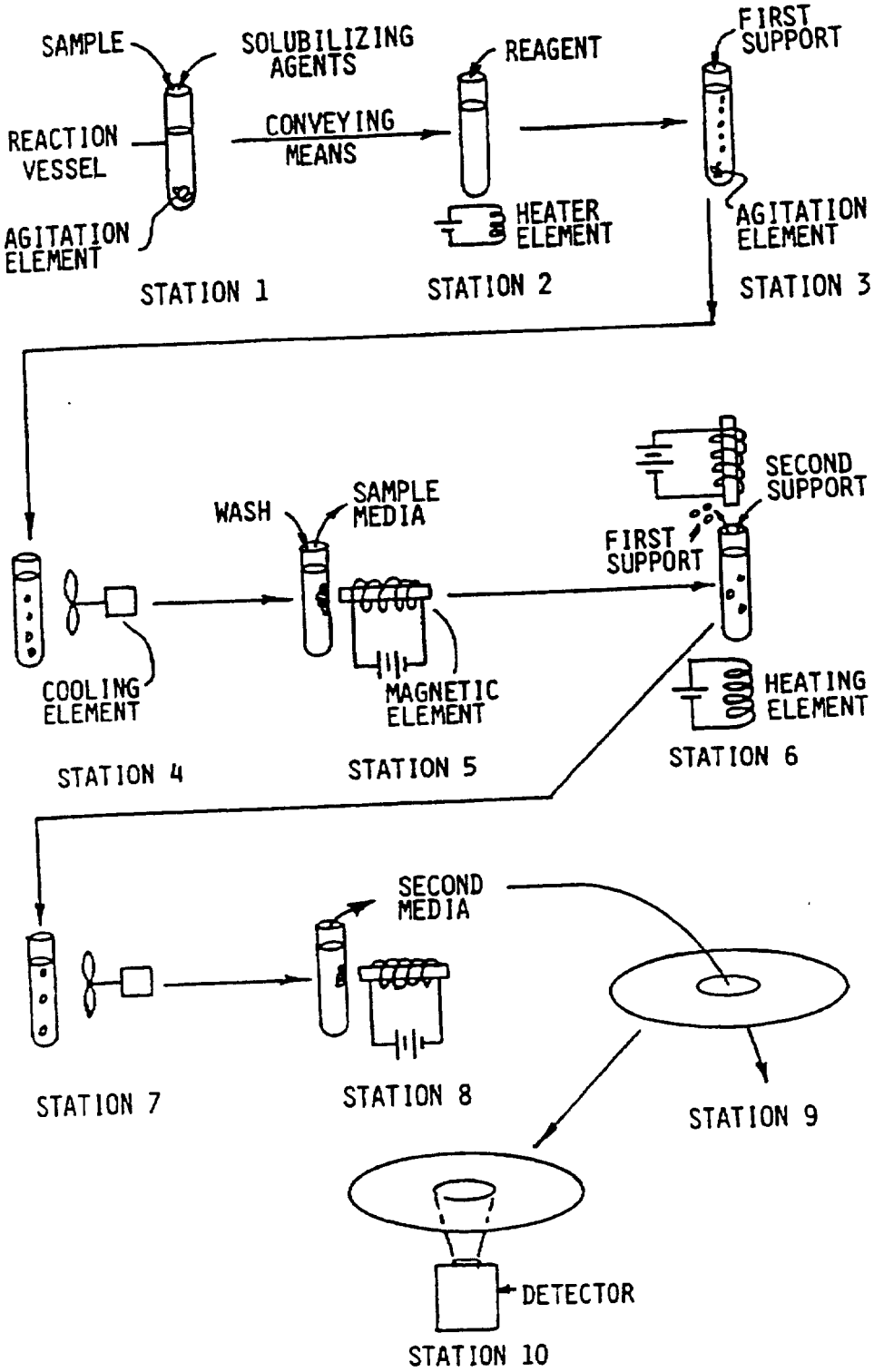

TARGET DNA IN ROUGH SAMPLE
CAPTURE PROBE
CAPTURE BEAD
STEP 1
BEAD
A
C'
B'
A'
COMPLEMENTARY HOMOPOLYMER TAILS
STEP 2
ISOLATE BEADS
TARGET DNA (SUBSTANTIALLY FREE OF SAMPLE IMPURITIES, DEBRI, EXTRANEOUS POLYNUCLEOTIDES)
STEP 3a
DNA POLYMERASE
HEXAMER PRIMERS
C' B' A'
C B A
STEP 3b
CORE RNA POLYMERASE
LOW SALT BUFFER
DNA
RNA
N
STEP 4
LABELLED PROBE
CAPTURE PROBE
SUPPORT
AMPLIFICATION TARGET
CAPTURE PROBE
SUPPORT
LABEL PROBE
TARGET/AMPLIFICATION PRODUCT
CAPTURE PROBE

FIG. 6



Ex. 8 Pg. 24

FIG. 7



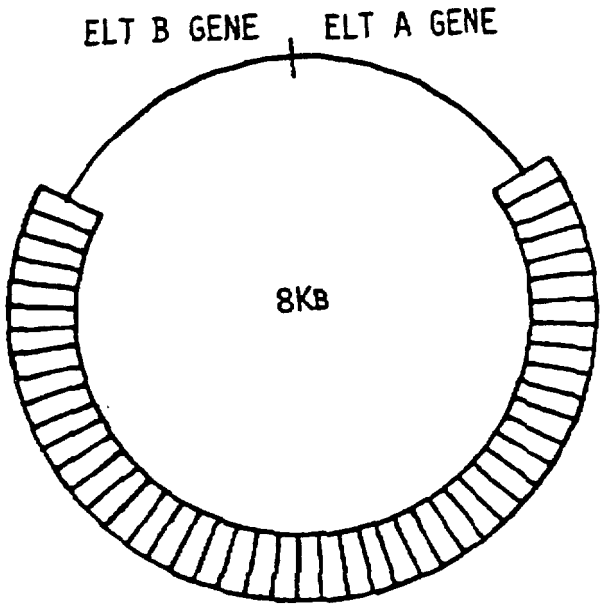


FIG. 8

TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS

This application is a divisional application of U.S. Ser. No. 08/400,657 filed Mar. 8. 1995; which is a continuation application of U.S. Ser. No. 08/257,469. filed Jun. 8. 1994 and now abandoned; which is a continuation application of U.S. Seral No. 08/124,826. filed Sep. 21. 1993 and now abandoned; which is a continuation application of U.S. Ser. No. 07/946,749 filed Sep. 17. 1992 and now abandoned; which is a continuation application of U.S. Ser. No. 07/648,468 filed Jan. 31. 1991 and now abandoned; which is a continuation-in-part application of U.S. Ser. No. 07/136,920 filed Dec. 21. 1987 and now abandoned; and which is a continuation-in-part application of U.S. Ser. No. 06/922,155 filed Oct. 23. 1986 and now abandoned. The disclosures of Ser. No. 07/136,920 and 06/922,155 are incorporated herein by reference.

BACKGROUND OF THE INVENTION

The present invention pertains to methods, reagents, compositions, kits, and instruments for use in capturing target molecules. In particular, the present invention relates to methods, reagents, compositions, and kits for capturing deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) from clinical samples. Embodiments of the present invention provide methods for rapid, sensitive detection of nucleic acid targets in clinical samples adaptable to non-radioactive labeling techniques and automation.

The following definitions are provided to facilitate an understanding of the present invention. The term "biological binding pair" as used in the present application refers to any pair of molecules which exhibit natural affinity or binding capacity. For the purposes of the present application, the term "ligand" will refer to one molecule of the biological binding pair and the term "antiligand" or "receptor" will refer to the opposite molecule of the biological binding pair. For example, without limitation, embodiments of the present invention have applications in nucleic acid hybridization assays where the biological binding pair includes two complementary strands of polynucleic acid. One of the strands is designated the ligand and the other strand is designated the antiligand. However, the biological binding pair may include antigens and antibodies, drugs, and drug receptor sites and enzymes and enzyme substrates.

The term "probe" refers to a ligand of known qualities capable of selectively binding to a target antiligand. As applied to nucliec acids, the term "probe" refers to a strand of nucleic acid having a base sequence complementary to a target strand.

The term "label" refers to a molecular moiety capable of detection including, by way of example, without limitation, radioactive isotopes, enzymes, luminescent agents, and dyes. The term "agent" is used in a broad sense, including any molecular moiety which participates in reactions which lead to a detectable response. The term "cofactor" is used broadly to include any molecular moiety which participates in reactions with the agent.

The term "retrievable" is used in a broad sense to described an entity which can be substantially dispersed within a medium and removed or separated from the medium by immobilization, filtering, partitioning, or the like.

The term "support" when used alone includes conventional supports such as filters and membranes as well as retrievable supports.

The term "reversible," in regard to the binding of ligands and antiligands, means capable of binding or releasing upon imposing changes which do not permanently alter the gross chemical nature of the ligand and antiligand. For example, without limitation, reversible binding would include such binding and release controlled by changes in pH, temperature, and ionic strength which do not destroy the ligand or antiligand.

The term "amplify" is used in the broad sense to mean creating an amplification product which may include by way of example, additional target molecules, or target-like molecules which are capable of functioning in a manner like the target molecule, or a molecule subject to detection steps in place of the target molecule, which molecules are created by virtue of the presence of the target molecule in the sample. In the situation where the target is a polynucleotide, additional target, or target-like molecules, or molecules subject to detecting can be made enzymatically with DNA or RNA polymerases or transcriptases.

Genetic information is stored in living cells in threadlike molecules of DNA. In vivo, the DNA molecule is a double helix, each strand of which is a chain of nucleotides. Each nucleotide is characterized by one of four bases: adenine (A), guanine (G), thymine (T), and cytosine (C). The bases are complementary in the sense that, due to the orientation of functional groups, certain base pairs attract and bond to each other through hydrogen bonding. Adenine in one strand of DNA pairs with thymine in an opposing complementary strand. Guanine in one strand of DNA pairs with cytosine in an opposing complementary strand. In RNA, the thymine base is replaced by uracil (U) which pairs with adenine in an opposing complementary strand.

DNA consists of covalently linked chains of deoxyribonucleotides and RNA consists of convalently linked chains of ribonucleotides. The genetic code of a living organism is carried upon the DNA strand in the sequence of the base pairs.

Each nucleic acid is linked by a phosphodiester bridge between the five prime hydroxyl group of the sugar of one nucleotide and the three prime hydroxyl group of the sugar of an adjacent nucleotide. Each linear strand of naturally occurring DNA or RNA has one terminal end having a free five prime hydroxyl group ad another terminal end having a three prime hydroxyl group. The terminal ends of polynucleotides are often referred to as being five prime termini or three prime termini in reference to the respective free hydroxyl group. Complementary strands of DNA and RNA form antiparallel complexes in which the three prime terminal end of one strand is oriented to the five prime terminal end of the opposing strand.

Nucleic acid hybridization assays are based on the tendency of two nucleic acid strands to pair at complementary regions. Presently, nucleic acid hybridization assays are primarily used to detect and identify unique DNA or RNA base sequences or specific genes in a complete DNA molecule, in mixtures of nucleic acid, or in mixtures of nucleic acid fragments.

The identification of unique DNA or RNA sequences or specific genes within the total DNA or RNA extracted from tissue or culture samples may indicate the presence of physiological or pathological conditions. In particular, the identification of unique DNA or RNA sequences or specific genes, within the total DNA or RNA extracted from human or animal tissue, may indicate the presence of genetic diseases or conditions such as sickle cell anemia, tissue compatibility, cancer or precancerous states, or bacterial or

viral infections. The identification of unique DNA or RNA sequences or specific genes within the total DNA or RNA extracted from bacterial cultures or tissue containing bacteria may indicate the presence of antibiotic resistance, toxins, viruses, or plasmids, or provide identification between types of bacteria.

Thus, nucleic acid hybridization assays have great potential in the diagnosis and detection of disease. Further potential exists in agriculture and food processing where nucleic acid hybridization assays may be used to detect plant pathogenesis or toxin-producing bacteria.

One of the most widely used nucleic acid hybridization assay procedures is known as the Southern blot filter hybridization method or simply, the Southern procedure (Southern, E., *J. Mol. Biol. I*, 98. 503. 1975). The Southern procedure is used to identify target DNA or RNA sequences. This procedure is generally carried out sheets. The immobilized sample RNA or DNA is contacted with radio-labeled probe strands of DNA having a base sequence complementary to the target sequence carrying a radioactive moiety which can be detected. Hybridization between the probe and the sample DNA is allowed to take place.

The hybridization process is generally very specific. The labeled probe will not combine with sample DNA or RNA if the two nucleotide entities do not share substantial complementary base pair organization standard. Hybridization can take from three to 48 hours depending on given conditions.

However, as a practical matter there is always nonspecific binding of the labeled probe to supports which appears as "background noise" on detection. Background noise reduces the sensitivity of an assay. Unhybridized DNA probe is subsequently washed away. The nitrocellulose sheet is placed on a sheet of X-ray film and allowed to expose. The X-ray film is developed with the exposed areas of the film identifying DNA fragments which have been hybridized to the DNA probe and therefore have the base pair sequence of interest.

The use of radioactive labeling agents in conjunction with Southern assay techniques have allowed the application of nucleic acid assays to clinical samples. Radioactive decay is detectable even in clinical samples containing extraneous proteinaceous and organic material. However, the presence of extraneous proteinaceous and organic material may contribute to nonspecific binding of the probe to the solid support. Moreover, the use of radioactive labeling techniques requires a long exposure time to visualize bands on X-ray film. A typical Southern procedure may require 1 to 7 days for exposure. The use of radioactive labeling agents further requires special laboratory procedures and licenses.

The above problems associated with assays involving radioisotopic labels have led to the development of techniques employing nonisotopic labels. Examples of nonisotopic labels include enzymes, luminescent agents, and dyes. Luminescent labels emit light upon exitation by an external energy source and may be grouped into categories dependent upon the source of the exciting energy, including: radioluminescent labels deriving energy from high energy particles; chemiluminescent labels which obtain energy from chemical reactions; bioluminescent labels wherein the exciting energy is applied in a biological system; and photoluminescent or fluorescent labels which are excitable by units of electromagnetic radiation (photons) of infrared, visual or ultraviolet light. See, generally, Smith et al., *Ann. Clin. Biochem.*, 18: 253. 274 (1981).

Nonisotopic assay techniques employing labels excitable by nonradioactive energy sources avoid the health hazards and licensing problems encountered with radioisotopic label assay techniques. Moreover, nonisotopic assay techniques hold promise for rapid detection avoiding the long exposure time associated with the use of X-ray film.

However, nonisotopic assays have not conveyed the sensitivity or specificity to assay procedures necessary to be considered reliable. In luminescent assays, the presence of proteins and other molecules carried in biological samples may cause scattering of the exciting light or may absorb light in the spectrum of emission of the luminescent label, resulting in a quenching of the luminescent probe.

In enzymatic assays, the presence of proteins and other molecules carried in biological samples may interfere with the activity of the enzyme.

Similarly, in colorimetric assays, the change in color may not be detectable over proteins and other materials carried in biological samples.

Embodiments of the present invention are concerned with target and background capture on supports and on retrievable supports including magnetic particles. Magnetic particles have been suggested as supports for the synthesis of organic compounds, including oligomers such as DNA, RNA, polypeptides, and other multiunit molecules that have a defined sequences. See, for example, European Patent Application No. 83112493.8 to Steven A. Benner and Genetics Institute. However, magnetic particles have not been suggested as retrievable supports for target capture and background removal.

Other utilization of magnetic particles has included magnetic fluids in the blood, R. Neubauer, *IEEE transactions on magnetics MAG-9*, 445 (1973); attachment of functional group for separation of biomolecules, U.S. Pat. No. 3,970. 518 to I. Giaver; labelling of cell-surface receptors, S. Margel et al., *Jour. Imm. Meth.* 28:341–53 (1979); attachment to drugs for magnetic targeting during therapeutic, A. Senyei et al., *J. App. Phys.*, 49 (6): 3578 (1978). K. Wieder et al., *Pro. Soc. of Exp. Bio. Med.*, 58:141 (1978), K. Mosbach and U. Shroeder, *FEBS letters* 102:112 (1979); selective separation of viruses, bacteria, and other cells, R. Molday et al., *Nature* 268:438 (1977); and incorporation of magnetic particles as support in gel affinity chromatography for biological polymers, K. Mosbach and L. Anderson, *Nature* 270:359 (1977), which are incorporated herein by reference.

The use of a two probe system to effect target capture on conventional non-retrievable supports has been suggested in an article authored by Ann-Christine Syuänen, Matti Laaksonen and Hans Söderlund entitled "Faster Quantification of Nucleic Acid Hybrids by Affinity-Based Hybrid Collection:" *Nucleic Acids Research*, 14(12): 5037 (1986).

SUMMARY OF THE INVENTION

It is an object of the present invention to provide methods, reagents, compositions, kits, and instrumentation for performing assays for target molecules of interest. Other objects will be presented hereinafter. For convenience, without limitation embodiments of the present invention can be grouped into areas of target capture, background capture, and combinations thereof.

Turning first to target capture, an embodiment of the present invention feature capture and release cycles to isolate target molecules. The method includes contacting a sample medium potentially containing target molecules with probes and a first support associated or capable of associating with at least one probe under binding conditions. The

probes are capable of selectively reversibly binding to the target molecules to form a complex including the probe target and the first retrievable support. Next, the support is separated from the sample medium and brought into contact with a second medium. Next, the support is subjected to releasing conditions to release the target from the support and the support is separated from the second medium. Next, a second support is contacted with the second medium under binding conditions. The second support is associated with or capable of associating with at least one probe capable of selectively binding to the target molecule. Under binding conditions, the target forms a complex with the probe associated to second support for further processing.

Preferably, the first support is retrievable in the sense that it is capable of substantially homogeneous dispersion within the sample medium and can be substantially physically separated, retrieved, or immobilized within the sample medium.

Separation of the first support from the first medium removes nonspecifically bound cellular debris attached to the first support. Further binding of the target molecule to a second support further concentrates the target for detection and permits further release-capture cycles for greater purification.

A further embodiment of the present method features a retrievable support. The method includes contacting the sample potentially carrying target nucleic acid with a retrievable support in association with a probe moiety. The retrievable support is capable of substantially homogenous dispersion within a sample medium. The probe moiety may be associated to the retrievable support, by way of example, by covalent binding of the probe moiety to the retrievable support, by affinity association, hydrogen bonding, or nonspecific association.

The support may take many forms including, by way of example, nitrocellulose reduced to particulate form and retrievable upon passing the sample medium containing the support through a sieve; nitrocellulose or the materials impregnated with magnetic particles or the like, allowing the nitrocellulose to migrate within the sample medium upon the application of a magnetic field; beads or particles which may be filtered or exhibit electromagnetic properties; and polystyrene beads which partition to the surface of an aqueous medium.

A preferred embodiment of the present invention includes a retrievable support comprising magnetic beads characterized in their ability to be substantially homogeneously dispersed in a sample medium. Preferably, the magnetic beads carry primary amine or carboxyl functional groups which facilitate covalent binding or association of a probe entity to the magnetic support particles. Preferably, the magnetic support beads are single domain magnets and are super paramagnetic exhibiting no residual magnetism. The first probe includes a probe ligand moiety capable of specifically binding to antiligand under binding conditions. The retrievable support is capable of substantially homogeneous dispersion within the sample media and includes at least one antiligand moiety capable of binding to ligand under binding conditions to form a target-probe support complex. Next, the retrievable support and sample medium are separated to allow the sample medium to be processed further.

Embodiments of the invention are suitable for capturing target molecules from a clinical sample medium containing extraneous material. The order of contacting the sample medium with probe or retrievable support is a matter of choice. However, the choice may be influenced by the kinetics of binding between the probe and target on one hand, and between the probe ligand and support antiligand on the other.

As applied to polynucleotide target molecules and homopolymer ligands and antiligands, the homopolymer ligand and antiligand binding is generally faster than probe binding to target. Probe binding to the target is sterically impaired after the probe ligand is bound to the support antiligand. A preferred embodiment includes contacting the sample medium with the reagent and bringing the mixture to hybridization conditions. Next, the retrievable support is dispersed in the reagent and sample medium allowing the formation of a target-probe complex in advance of the formation of probe support complexes.

A further embodiment of the present invention features a multiple probe system.

Preferably the method includes a reagent including a first probe as previously described and at least one second probe capable of binding to the target molecule and having label moieties capable of detection. The second probe is capable of forming a target (first and second) probe-support complex. The step of separating the retrievable support from the sample medium not only removes extraneous material from the target-(first and second) probe-support complex, but also separates any second probe which is not bound to the target. Second probe unbound to target contributes to background noises, false signals indicating the presence of target.

Further processing may include release of the target (first and second) probe complex from the retrievable support into a second medium and rebinding of the target (first and second) probe complex to new support. The first retrievable support may carry nonspecifically bound materials which can interfere with assay procedures. Thus, after the release of the target-probe complex from the retrievable support and the retrievable supports removal, a second support having an antiligand moiety capable of binding to the probe ligand can be brought into contact with the target-probe complex under binding conditions to effect a further cycle of target-probe binding or capture for further purification and concentration of target-probe complex.

Further processing may include background capture. A further embodiment of the present invention includes a method wherein the second probe has a second ligand moiety. The method further includes a background support having a second antiligand moiety. The second ligand moiety and second antiligand moiety are capable of stably binding under binding conditions only when the second probe is unbound to the target molecule. The method further includes the step of contacting a medium potentially containing second probe unbound to target with a background support under binding conditions. Next, the background support is separated from the medium to remove unbound second probe reducing background noise.

The term "background support" is used in the conventional sense to include filters and membranes as well as retrievable supports. Binding to the background support does not need to be releasible.

A preferred retrievable support includes, by way of example without limitation, particles, grains, beads, or filaments capable of dispersion within and separation from a medium. Methods of separation include by way of example, without limitation, of filtration, centrifugation, precipitation, surface floatation, settling, or the introduction of electromagnetic fields.

The present method can be applied to polynucleotide target molecules. Preferably, the first and second probes bind

quickly to a polynucleotide target "in solution" as opposed to the situation where either the target or probe is immobilized.

The retrievable support, capable of substantial dispersion within a solution, permits interactions between the retrievable support and probes which mimic "in solution" hybridization. In solution, hybridiation can be completed in approximately 3–15 minutes. The rapid hybridizations and simplicity of the present methods permit automation. The present method allows nucleic acid sequences contained in clinical samples to be separated from extraneous material allowing the methods to be applied to nonisotopic labeling techniques.

An embodiment of the present method where the target molecule is a polynucleotide, includes contacting a sample medium with reagent under binding conditions. The reagent includes at least one first polynucleotide probe and at least one second polynucleotide probe. The first probe is capable of forming a complex with the target molecule and has a first homopolymer ligand moiety. The second probe is capable of forming a complex with the target molecule in addition to the first probe. The second probe includes a label moiety which has a second homopolymer ligand moiety which is different than the first homopolymer ligand of the first probe. Next, the reagent and sample medium are contacted with a background support and a target capture support. The background support includes at least one second homopolymer antiligand moiety capable of binding to the second homopolymer ligand moiety of the second probe when said second probe is unbound to target. The target capture support includes at least one first homopolymer moiety capable of binding to the first homopolymer ligand moiety of the first probe. The background support and the target capture support remove background noise and the target capture support further concentrates the target-(first and second) probe complex for further processing and separates the target-(first and second) probe complex from cellular debris. Further processing includes the detection of the label moiety indicative of the presence of the target molecule.

Turning now more specifically to embodiments of the invention pertaining to background capture, one embodiment includes a method wherein probe and target are allowed to form a complex. Next, uncomplexed probe is brought into contact with a support under binding conditions. The support is capable of selectively binding unbound probe. Next, the support is separated from the probe-target complex.

A still further embodiment of the present invention includes a method of separating a plurality of target molecules for further processing.

One embodiment includes the sequential addition and removal of probes specific to target molecules on a plurality of supports. A further embodiment includes a method which includes contacting a sample with a first series probe and capturing the target and probe on a plurality of supports. The first series probe includes a ligand capable of association with the support. The first probe series includes probes for all plurality targets which are capable of binding to supports specific for each target molecule. The supports are capable of being separated from each other, the separation of which results in individual types of target molecules being isolated with the support.

A further embodiment of the present invention includes a reagent composition. The reagent composition includes a first probe and a second probe. The first probe is capable of forming a complex with a target molecule and includes a probe ligand moiety capable of specifically binding to antiligand under binding conditions. The second probe is capable of forming a complex with the target molecule and includes a label moiety capable of detection. The reagent composition can be used to capture and detect the target in a sample medium when used with a retrievable support having antiligand moieties.

A further embodiment of the present reagent composition includes a second probe having a second ligand moiety capable of stably binding to an antiligand only in the situation where the second probe is unbound to the target molecule. The reagent composition allows background noise to be reduced by contacting sample potentially containing an unbound second probe with a background support having a second antiligand moiety.

A further embodiment includes a support capable of substantially homogeneous dispersion in a sample medium having oligonucleotide antiligands adapted for binding to oligonucleotide ligands on probes.

A preferred embodiment of the support includes, by way of example, particles, grains, filaments, and beads capable of separation. Means of separation include, by way of example without limitation, precipitation, settling, floatation, filtration, centrifugation, and electromagnetism.

A preferred embodiment includes polystyrene beads, between 10–100 microns in diameter, which are capable of substantially homogeneous dispersion and separation from a medium by filtration or floatation. Another preferred embodiment includes ferromagnetic beads. A ferromagnetic bead marketed under the trademarks BIO-MAG is capable of substantially homogeneous dispersion in an aqueous medium and can be retrieved or immobilized by an electromagnetic field. The ferromagnetic bead includes an iron core which is coated with an amine reactive covering. The beads are generally spherical and have a diameter of one micron. The polystyrene and ferromagnetic beads are treated to include antiligand moieties.

A further embodiment of the present invention includes a kit for performing assays for target molecules which are part of a biological binding pair. In the case where the target is a polynucleotide having a specific base sequence, the kit includes a reagent wherein the reagent includes a first polynucleotide probe and a second polynucleotide probe. The first and second probes are capable of binding to mutually exclusive portions of the target to form a complex in which both probes are bound to the target. The first probe is capable of reversibly binding to a first support under binding conditions, and the second probe includes a label moiety capable of detection. The kit further includes a first support allowing the support to form complexes with the target and probes which can be selectively separated from the sample medium.

A further embodiment of the present kit includes a second probe and a background support. The second probe, when not bound to the target, is capable of selectively binding to a background support. The background support is capable of being separated from a medium containing reagent to remove the nonspecifically bound second probe.

A further embodiment of the present invention includes an instrument for performing assays in accordance with the present method. In the situation where the target is a polynucleotide, the instrument includes a reaction chamber adapted for receiving reagent and target in a substantially mixed homogeneous state. The reagent includes a first and a second polynucleotide probe. Each probe is capable of binding to mutually exclusive portions of the target forming

a complex in which both probes are bound to the target. The first probe is capable of reversibly binding to a first support under binding conditions and the second probe includes a label moiety capable of detection. The instrument further includes means for contacting a first support with the reagent and sample to allow the first probe and target-probe complex to become bound to the support. The instrument further includes means for bringing the sample, reagent, and support to binding conditions to form target-probe complexes bound to support. The instrument further includes means for bringing the first probe into releasing conditions. Finally, the instrument includes means for separating the support from the sample and from the reagent.

The term "reaction vessel" is used in a broad sense to include any means of containment including, by way of example without limitation, cuvettes, test tubes, capillaries, and the like.

Suitable means for bringing the sample, reagent, and support into binding conditions or bringing reagent and support into releasing conditions include by way of example, temperature controls which can elevate or lower the temperature of the sample, reagent, and support to selective denature or anneal polynucleotide strands.

Suitable means for separating the support from the reagent or sample include by way of example, electromagnets for use in conjunction with magnetic beads, fibers affixed to an anchoring support, centrifuges for use with polystyrene grains, and the like.

Further embodiments of the present invention include means for bringing the reagent and target into contact with background support under binding conditions to remove any second probes having label moieties which second probes are not specifically bound to the target.

Embodiments of the present instrument adapted for use with luminescent label moieties include suitable label excitation means. Instruments for use with fluorescent label moieties include lasers or light emitting assemblies with filters to define appropriate wave lengths. Instruments for use with chemiluminescent label moieties include injection apparatus for injecting cofactors into the reaction chamber.

The invention also features a method for assaying a sample for a target polynucleotide, which sample contains the target polynucleotide and non-target polynucleotides, the method involving contacting the sample with a polynucleotide probe capable of forming a complex with the target polynucleotide, substantially separating the complex from the non-target polynucleotides in the sample, amplifying the target polynucleotide, to form an amplification product, and measuring or detecting the amplified target polynucleotide. This method advantageously can be used in conjunction with the target capture and background capture steps described above.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1–3 are flow diagrams illustrating steps, apparatus, and reagents used in methods of the invention. The term "FIG. 1" refers collectively to FIG. 1*a* and FIG. 1*b*. Similarly, the term "FIG. 2" refers collectively to FIG. 2*a* and FIG. 2*b*.

FIG. 4–6 are diagrammatic representations of capture amplification methods of the invention.

FIG. 7 is a diagram illustrating features of an apparatus made in accordance with one embodiment of the present invention.

FIG. 8 is a diagrammatic representation of a genetic construction used in the invention.

DETAILED DESCRIPTION

Turning now to the drawings, which by way of illustration depict preferred embodiments of the present invention, and in particular FIG. 1, a method of procedure, with necessary reagent compositions, is illustrated in schematic form for an assay for target polynucleotide strands. Conventional assay technique include many target strands, and many probe strands would be used to performs an assay. However, for the simplicity to further an understanding of the invention, the illustration depicts only limited numbers of probes, support entities, and targets. FIG. 1 features a method utilizing retrievable supports.

Step 1 of the assay illustrated in FIG. 1 begins with a clinical sample which, by way of illustration, contains cells. The cells potentially carry target nucleic acid, either DNA or RNA, having a base sequence of particular interest indicative of pathogens, genetic conditions, or desirable gene characteristics. The clinical samples can be obtained from any excreta or physiological fluid, such as stool, urine, sputum, pus, serum, plasma, ocular lens fluid, spinal fluid, lymph, genital washings, or the like. Individuals skilled in the art may desire to reduce biopsy samples to single cell suspensions or small clumps by means known in the art. For example, biopsy samples of solid tissues can be effectively reduced to single cell suspensions or to small clumps of cells by agitating the biopsy sample in a mixture of 0.5M sodium chloride, 10 mM magnesium chloride, 0.14M phosphate buffer, pH 6.8, and 25 Mg/ml cyclohexamide. Isolation of specific cell types by established procedures known in the art, such as differential centrifugation, density gradient centrifugation, or other methods, can also be applied at this step.

The cells are then treated to liberate their DNA and/or RNA. Chemical lysing is well known in the art. Chemical lysing can be performed with the dilute aqueous alkali, for example, 0.1 to 1.0M sodium hydroxide. The alkali also serves to denature the DNA or RNA. Other denaturization and lysing agents include elevated temperatures, organic reagents, for example, alcohols, amides, amines, ureas, phenols and sulfoxides, or certain inorganic ions, for example chaotropic salts such as sodium trifluoroacetate, sodium trichloroacetate, sodium perchlorate, guanidinium isothiocyanate, sodium iodide, potassium iodide, sodium isothiocyanate, and potassium isothiocyanate.

The clinical sample may also be subjected to various restriction endonucleases to divide DNA or RNA into discrete segments which may be easier to handle. At the completion of the sample processing steps, the clinical sample includes sample nucleic acid, cellular debris, and impurities. In the past, sample nucleic acid was separated from cellular debris and impurities by nonspecific binding of the nucleic acid to filters or membranes and washing cellular debris and impurities from the filter or membrane. However, in practice, some cellular debris and some impurities, as well as nontarget nucleic acid, are nonspecifically bound to the filter or membrane and are not removed by washes.

An embodiment of the present invention, as illustrated in Step 1, includes contacting the sample potentially carrying target nucleic acid with a retrievable support in association with a probe moiety. The retrievable support is capable of substantially homogenous dispersion within a sample medium. The probe moiety may be associated to the retrievable support, by way of example, by covalent binding of the probe moiety to the retrievable support, by affinity association, hydrogen binding, or nonspecific association.

The support may take many forms including, by way of example, nitrocellulose reduced to particulate form and

retrievable upon passing the sample medium containing the support through a sieve; nitrocellulose or the materials impregnated with magnetic particles or the like, allowing the nitrocellulose to migrate within the sample medium upon the application of a magnetic field; beads or particles which may be filtered or exhibit electromagnetic properties; and polystyrene beads which partition to the surface of an aqueous medium.

A preferred embodiment of the present invention includes a retrievable support comprising magnetic beads characterized in their ability to be substantially homogeneously dispersed in a sample medium. Preferably, the magnetic beads contain primary amine functional groups which facilitate covalent binding or association of a probe entity to the magnetic support particles. Preferably, the magnetic support beads are single domain magnets and are super paramagnetic exhibiting no residual magnetism.

The particles or beads may be comprised of magnetic particles, although they can also be other magnetic metal or metal oxides, whether in impure, alloy, or composite form, as long as they have a reactive surface and exhibit an ability to react to a magnetic field. Other materials that may be used individually or in combination with iron include, but are not limited to, cobalt, nickel, and silicon. Methods of making magnetite or metal oxide particles are disclosed in Vandenberghe et al., "Preparation and Magnetic Properties of Ultrafine Cobalt Ferrites," *J. of Magnetism and Magnetic Materials*, 15 through 18: 1117–18 (1980); E. Matijevic, "Mono Dispersed Metal (Hydrous) Oxide—A Fascinating Field of Colloidal Science," *Acc. Chem. Res.*, 14:22–29 (1981), the disclosures which are incorporated herein by reference.

A magnetic bead suitable for application to the present invention includes a magnetic bead containing primary amine functional groups marketed under the trade name BIO-MAG by Advanced Magnetics, Inc. A preferred magnetic particle is nonporous yet still permits association with a probe moiety. Reactive sites not involved in the association of a probe moiety are preferably blocked to prevent nonspecific binding of other reagents, impurities, and cellular material. The magnetic particles preferably exist as substantially colloidal suspensions. Reagents and substrates and probe moieties associated to the surface of the particle extend directly into the solution surrounding the particle. Probe moieties react with dissolved reagents and substrates in solution with rates and yields characteristic of reactions in solution rather than rates associated with solid supported reactions. Further, with decreasing particle size the ratio of surface area to volume of the particles increases thereby permitting more functional groups and probes to be attached per unit weight of magnetic particles.

Beads having reactive amine functional groups can be reacted with polynucleotides to covalently affix the polynucleotide to the bead. The beads are reacted with 10 percent glutaraldehyde in sodium phosphate buffer and subsequently reacted in a phosphate buffer with ethylene-diamine adduct of the phosphorylated polynucleotide in a process which will be set forth in greater detail in the experimental protocol which follows.

Returning now to Step 2, the retrievable support with associated probe moieties is brought into contact with clinical sample and, progressing through to Step 3, is brought into binding conditions. The probe moiety specific for the target of interest becomes bonded to the target strands present in the clinical sample. The retrievable support, dispersed throughout the sample and reagent medium, allows the probe moieties and target to hybridize as though they are free in a solution.

Hybridizations of probe to target can be accomplished in approximately 15 minutes. In contrast, hybridizations in which either the probe or target are immobilized on a support not having the capability to be dispersed in the medium may take as long as 3to 48 hours.

Extraneous DNA, RNA, cellular debris, and impurities are not specifically bound to the support. However, as a practical manner, a small amount of extraneous DNA, RNA, cellular debris, and impurities are able to and do in fact nonspecifically bind to any entity placed within the reaction vessel including the retrievable support. Embodiments of the present invention facilitate the further purification of clinical samples to remove extraneous DNA, RNA, cellular debris, and further impurities from target polynucleotides.

Step 4 of FIG. 1 depicts the separation of the support of the clinical sample and the suspension of the support into a second medium. The second medium thus includes the retrievable support with the associated probe bound to target polynucleotide strands. Also carried with the retrievable support is extraneous DNA, RNA, cellular debris, and impurities nonspecifically bound to the support, but in a much lower concentration than what was initially found in the clinical sample. Those skilled in the art will recognize that some undesirable materials can be reduced by washing the support prior to suspension in the second medium.

The retrievable support with associated probe and target strands suspended in the second medium is subject to further denaturation as set forth in Step 5 thereby allowing the target to disassociate from the probe moieties of the retrievable support. The denaturation process may or may not release nonspecifically bound extraneous DNA, RNA, cellular debris, or impurities from the retrievable support. However, Step 5 of the present method allows the retrievable support to the removed from the second medium carrying with it much of the nonspecifically bound cellular debris, impurities, and extraneous DNA, and RNA initially carried over from the first clinical sample medium.

As set forth in Step 6, a new support can be introduced into the second medium under binding conditions to again capture target polynucleotide strands on probe moieties associated with the retrievable support. It will be recognized by those skilled in the art that the new support may actually include the original retrievable support after recycling steps to further purify and remove nonspecifically bound DNA, RNA, cellular debris, and impurities. Thus, the only impurities present in the second medium include DNA, RNA, cellular debris, and impurities previously nonspecifically bound to the support which has subsequently been released from the first support and dissolved or suspended in the second medium.

However, such impurities can be further removed from the target polynucleotides by removing the second retrievable support from the second medium and again repeating the cycle of introducing the retrievable support into a further medium, denaturation, and removal of the old support. Those skilled in the art will recognize that the magnetic beads described in the present invention are susceptible of being raised out of a solution or being held in place as a solution is removed or added to a containment vessel.

The ability of the magnetic beads to participate in the reactions which mimic "insolution kinetics" strands allow the completion of a cycle of denaturation and binding to the target to be accomplished in three to fifteen minutes.

After sufficient purification and concentration, the target can be detected by luminescent or radioactive methods

known in the art as indicated in Step 8. Purification of the medium containing the target allows the detection of nonisotopic label moieties without cellular debris and impurities.

Turning now to FIG. 2, which features a multiple probe method, a further embodiment to the present assay method is illustrated beginning with a clinical sample containing polynucleotide target which is processed in accordance with the clinical sample of the previous figure with the introduction of solubilizing agents and reagent. The reagent of the assay method depicted in FIG. 2 includes a first polynucleotide probe strand (P_1) and a second polynucleotide probe strand (P_2) capable of forming a complex with the target in which both probes (P_1 and P_2) are bound to the target. The first probe (P_1) is capable of associating with a retrievable support (S_1) under binding conditions. The second probe has at least one label moiety capable of detection. The label moiety is illustrated in the drawings with an asterisk or a star. Following the introduction of a solubilizing agents and reagent under denaturation conditions, the solution containing the clinical sample potentially includes target polynucleotides and reagent in the form of the first and second probes, plus cellular debris, solubilizing agents, impurities, and extraneous RNA and DNA.

Under binding conditions as illustrated in Step 2, the first and second probes ($P_1$and P_2) bind to mutually exclusive portions of the target. The hybridization of the probes (P_1 and P_2) to the target in solution is rapid and unimpaired by association with a solid support. In order to insure the binding of the target to the first and second probe strands (P_1 and P_2) an excess of probe is employed. However, even if an excess of probe (P_1 and P_2) were not employed, some probe would fail to find target and would remain unhybridized in the sample medium. The unhybridized second probe (P_2) having a label moiety constitutes background noise if present during detection.

The first probe (P_1) is capable of binding to a support (S_1) by means of a ligand capable of binding to an antiligand moiety on a support. The ligand (L_1) includes, by way of example, a tail portion comprising a homopolymer. The support (S_1) includes an antiligand (A_1) capable of receiving and binding to ligand (L_1). The antiligand (A_1) includes, by way of example, a homopolymer complementary to the ligand (L_1) of probe (P_1).

Turning now to Step 3, under binding conditions the antiligand moiety (A_1) of support (S_1) associates or binds to the ligand moiety (L_1) of the first probe (P_1) which is itself bound to the target and linked to the second probe (P_2). The support may take many forms. Beads or particulate supports can e dispersed in solution and participate in binding with target probe reactions which demonstrate near in solution kinetics. Further, retrievable beads and particulate supports can separate probe-target complexes from nondissolvable debris without clogging problem inherent in more conventional filters or membranes.

However, conventional membranes, filters, or cellulose supports may also be employed for some applications in which clogging may not be a problem. Due to the rapid hybridization of the probes to target insolution, a solid nonbead or nonparticulate membrane or filter support can be incorporated into the reaction vessel. The solution of reagent and sample can be passed through the support to affect target capture. The support (S_1) is illustrated in FIG. 2 as a retrievable support.

In solution with the target-probe support complex are unbound first and second probe moieties, unbound target solubilizing agents, im[illegible]ities, and cellular debris. The unbound second probe (P_2) which has label moieties constitutes noise, producing a signal which mimics the presence of target. A small amount of extraneous cellular debris, solubilizing agents, impurities, and probes may also become nonspecifically bound to the retrievable support.

In Step 4, the support (S_1) is separated from the clinical sample medium. If a retrievable support is used, separation can be accomplished either by immobilizing the retrievable support within a reaction vessel or by withdrawing the retrievable support from the sample medium directly. Those skilled in the art will recognize that the immobilized support can be washed to reduce undesirable material.

Turning now to Step 5, the target-probe support complex is substantially free of extraneous RNA, DNA, solubilizing agents, impurities, and cellular material and can be monitored for the presence of the label moieties indicative of the presence of the target molecule. However, a small amount of extraneous DNA, RNA, solubilizing agents, impurities, and cellular materials may still be nonspecifically bound to the support (S_1). Moreover, unbound, in the sense that it is not associated with target, second probe (P_2) may also be nonspecifically bound to the support (S_1) and can affect signals from nonisotopic label moieties. The presence of unbound second probe moiety (P_2) having label moieties is a significant cause of background noise thereby reducing the accuracy of the assay procedure.

Thus, as an alternative Step 5, the first support (S_1) may be suspended into a second medium where the support (S_1) is separated from the target-probe complex by denaturation.

Following denaturation, in Step 6, the first support (S_1) is removed from the second medium and replaced with a second support (S_2). The second support (S_2) includes an antiligand moiety (A_1) capable of binding to the ligand moiety (L_1) of the first probe.

Moving to Step 7, under binding conditions, the target-probe complex reassociates with the second support (S_2). The removal of the first support (S_1) removes extraneous material, debris, and probes nonspecifically bound to the first support (S_1) from the assay medium.

As illustrated in Step 8, the medium containing the target-probe complex can be monitored for the presence of the labels. However, further purification of the assay medium can be performed to further reduce the presence of background and extraneous materials which may have been carried from the sample medium nonspecifically bound to the first retrievable support (S_1) and subsequently dissolved or disassociated from the first support (S_1) into the second medium.

Thus, the second retrievable support (S_2) may be brought into contact with a third medium, the medium brought into conditions to release the target-probe complex from the support, and the support removed to complete a further cycle. The number of cycles will be a matter of choice depending on the type of sample, type of label moieties, and the sensitivity of the detection equipment. Different types of supports may be used at different times. Thus, a retrievable support can be used to gather or concentrate the target-probe complexes from sample mediums or solutions initially to avoid problems of clogging typical of membranes or filters. The second or third supports preferably includes a membrane or filter with antiligand moieties (A_1) which bind to the ligand moiety (L_1) of the first probe (P_1). Membrane or filter supports can simplify process steps allowing flow-through recovery of target-probe complexes.

A further embodiment of the present invention is particularly well suited for reducing background noise. Referring

now to FIG. 3, a modification of the previous assay procedure illustrated in FIG. 2 is described. In FIG. 3, a target polynucleotide has formed a complex with a first and second probe moiety (P_1 and P_2) similar to the probe moieties described in FIG. 2. However, the second probe includes a second ligand (L_2). The second ligand (L_2) may include, by way of example, a single terminal ribonucleotide which complexes with a borate antiligand, an alternating copolymer which binds with a complementary copolymer, a biotin ligand which binds to an avidin antiligand, or as illustrated, homopolymer ligand (L_2), and a complementary homopolymer antiligand (A_2).

Turning now to Step 1, a background support capable of selectively binding to the second probe (P_2), only when it is not bound to a target, is brought into contact with the medium containing the target-probe complex. The medium further includes free, disassociated first and second probes (P_1 and P_2). The labeled second probe (P_2), which contributes to the background noise, is specifically bound to the background support (B_1) by a vast molar excess of antiligand moieties (A_2) associated with the background support (B_1). Following binding of the unbound labeled probe (P_2) to the background support (B_1), the background support (B_1) is removed from the medium as illustrated in Step 2. The medium containing the target-probe complex can be monitored for the presence of the label contained upon the second probe (P_2) with a reduction in background noise. Alternatively, the medium containing the target-probe complex can be subjected to further processing.

The further processing can include further background reduction by repeating Steps 1 and through 3 described in FIG. 3 or, steps previously described in conjunction with FIG. 2. For example, background reduction steps can be incorporated into the processing of a clinical sample as illustrated in FIG. 2 at any point in which the ligand and antiligand moieties of the first and second probes do not interfere, and the target is complexed with the first and second probes.

An embodiment of the present method can practiced with additional amplification steps to generate an amplification product to improve the sensitivity of the assay. Turning now to FIGS. 4, 5, and 6, each Figure includes a Step 1 wherein target is captured with the use of a capture probe and a retrievable support in the form of a bead. The polynucleotide target includes areas defined as a^1, b^1, and c^1. The polynucleotide probe includes an area, "a" capable of binding to its complement "a^1" of the target. The probe further includes a ligand capable of binding to an antiligand associated with the bead. As illustrated, the ligand of the probe and the antiligand of the bead are complementary homopolymers.

In Step 2 of FIGS. 4, 5, and 6, the target is separated from extraneous polynucleotides, impurities, cellular material, and solubilizing reagents from sample processing procedures.

In Step 3 of FIGS. 4, 5, and 6, the isolated target is non-specifiably amplified to form a multitude of amplification products.

FIG. 4, Step 3, depicts amplification of the target DNA to form an amplification product subject to detection, complementary RNA, through the enzyme, core RNA polymerase. In FIG. 4, Step 3, the capture probe is complexed or coated with recA protein to facilitate probe target binding. Core RNA polymerase forms RNA complementary to the DNA target template. As the enzyme reads through the target sequences, the RNA probe area "a" and subsequent new nucleotide sequences are removed from the target which is able to bind to new recA coated probes to form a multitude of RNA polynucleotides having an area "c" which can be detected. The integer "n" represents a plurality of amplification products.

In the situation where the target is RNA, such as ribosomal RNA (rRNA) or messenger RNA (mRNA) the target RNA can be replicated nonspecifically by denaturing the RNA and subjecting the RNA to an enzyme such as Qβ replicase or reverse transcriptase.

FIG. 5 illustrates the application of a two enzyme amplification system. In Step 3(a) of FIG. 5, DNA polymerase is used in conjunction with hexamer primers to generate DNA segments which are complementary to the target. In Step 3(b), core RNA polymerase is used to form additional RNA complements to both target DNA and DNA target complements.

FIG. 6 illustrates the application of an enzymatic amplification system based on the enzyme DNA polymerase. Thus, in step 3(a), the target, separated from extraneous polynucleotides, impurities and debris, is subjected to DNA polymerase in conjunction with non-specific hexamer primers. The DNA polymerase generates DNA segments which are complementary to the initial target. The new DNA product, formed from the target DNA, is also a substrate for replication. The target and complements are subjected to cycling steps to denature the target and target complements and to add new enzyme to create new copies of the target and the target complement.

Following formation of the enzyme product, Step 4 of FIGS. 4–6 illustrates capture of the target and/or enzyme product as previously described with a further probe and support. The target and/or enzyme reaction product are amenable for further process steps including detection.

An embodiment of the present methods may be practiced with an aid of apparatus set forth in schematic form in FIG. 7. The apparatus includes the following major elements: at least one containment vessel, means for controlling the association of a probe with a target molecule and a retrievable support, means for separating the retrievable support from a sample solution, and means for releasing the target molecule from the retrievable support. These major elements may take various forms and are described more fully below.

The apparatus will be described below for illustration purposes as applying the methods described in FIGS. 2 and 3 relative to a target molecule which includes a polynucleotide. Thus, at Station 1, a clinical sample is placed within the containment vessel with solubilizing agents such as chaotropic salts, enzymes, and surfactants in order to dissolve cellular material and release nucleic acids. The containment vessel may include agitation elements to facilitate the break up of cells. The containment vessel may include any type of vessel, tube, cuvette suitable for containing the sample.

In an instrument designed for automated analysis, the apparatus set forth in FIG. 7 will preferably include means for receiving a plurality of containment vessels. For illustration purposes, the containment vessels containing the sample are analyzed sequentially. Thus, containment vessels are conveyed to a first station and then to subsequent stations where various steps of the assay method are performed.

The various stations are linked by conveying means. Conveying means may include a rotatable turntable, conveying belt, or the like. As applied in a clinical hospital setting, conveying means may include manual movement. Thus, hospital staff may obtain a tissue sample from a

patient and place the sample in the containment vessel. Sample processing, including the breakup of the tissue sample and initial mixing of solubilizing agents and reagents would be initiated at bedside and continued as the containment vessel traveled to a subsequent station for further processing. Reference to stations are for illustration purposes. Those skilled in the art will recognize that certain stations or steps may be combined or reversed.

Returning now to the first station, sample and solubilizing agents are placed within a containment vessel in which an agitation element thoroughly mixes the sample and solubilizing agents, releasing nucleic acids from cellular materials. Conveying means carry the containment vessel to Station 2 where the containment vessel receives reagent.

The reagent includes a first polynucleotide probe and a second polynucleotide probe. The first and second probes are capable of forming a complex with the target polynucleotides in which both probes are bound to mutually exclusive portions of the target. The first probe is also capable of binding to a retrievable support under binding conditions. The second polynucleotide probe includes a label moiety capable of detection. The reagent and sample nucleic acid are denatured by a heating element and conveyed to Station 3.

At Station 3, the containment vessel receives a first support depicted by open circles. The first support is homogeneously dispersed within the sample medium by suitable means including an agitation element. Examples of suitable supports include, without limitation, polystyrene beads, magnetic beads and other particulate or filamentous substances. As illustrated, the first support includes a magnetic bead having polynucleotide antiligands of deoxythymidine (dT). The first probe includes a tail portion of deoxyadenosine (dA) capable of binding to the first support during binding or hybridization conditions.

Moving to Station 4 hybridization conditions are imposed upon the sample medium by cooling by a cooling element. However, those skilled in the art will recognize that means to alter salt concentrations can be readily substituted for thermal controls. Thus, the target polynucleotide forms a complex with the first and second probes. Further, the homopolymer deoxyadenosine (dA) tail portion of the first probe hybridizes to the deoxythymidine (dT) homopolymer of the retrievable support.

From Station 4, the containment vessel is moved to Station 5 where the retrievable support is immobilized on the wall of the containment vessel by activating a magnetic element. If polystyrene beads were substituted for magnetic beads, the polystyrene bead would be immobilized by filtering or density differences. The sample medium is disposed of carrying with it most of the extraneous DNA, RNA, solubilizing agents, cellular material, and impurities. The immobilized retrievable support is washed to further remove extraneous DNA, RNA, solubilizing agents, cellular materials, and impurities.

Further, although it is illustrated that the retrievable support is immobilized on the wall of the reaction vessel, it is also possible to remove the retrievable support from the reaction vessel by a magnetic element and dispose of the first reaction vessel containing with it extraneous DNA, RNA, solubilizing agents, and cellular material which may be nonspecifically bound to the reaction vessel walls.

The retrievable support is placed in a second medium, either the same containment vessel or a new containment ves . The containment vessel, containing the retrievable support in a second medium is carried to Station 6.

At Station 6, the second medium is brought to denaturization conditions by suitable means including a heating element. The denaturization process releases the target-first and second-probe complex from the (dT) homopolymer of the retrievable support. The first support, potentially carrying extraneous DNA, RNA, impurities, and cellular material, is removed from the second medium. If desired, amplification steps may be applied to the target, now substantially free of impurities, debris, and non-target polynucleotides. Amplification steps may include the generation of an amplification product with enzymes such as, by way of example, DNA polymerase, RNA polymerase, transcriptases, or Qβ replicase. In the event the amplification product is not the target molecule, the second probe is directed to the amplification product as well as a third capture probe which takes the place of the first probe. A background support is then brought into contact with the second medium and passed to Station 7.

At Station 7 a cooling element brings the second medium to hybridization temperatures. The background support includes a second antiligand capable of specifically binding to a ligand carried upon the second probe. For example, without limitation, a terminal nucleotide of the second probe can be synthesized to be a ribo derivative which specifically binds to borate moiety carried upon the second support. The second probe bound to the target as part of a probe target complex will not bind to the borate carried upon the third support due to stearic hindrances. However, unbound second probe will specifically bind to the borate support. Alternatively, the second probe may include a homopolymer such as deoxycytosine (dC) which binds to a deoxyguanine (dG) homopolymer linker on a second support. The length of the homopolymers are designed such that complexes of the target-first and second probes with the second support are not stable; however, complexes of the second probe alone with the second support are stable within reaction parameters. Indeed, background capture binding of background support to unbound second probe can be irreversible.

Next, the containment vessel containing the second medium and the background support is conveyed to Station 8 where the background support having second probe strands unbound to the target-probe complex is separated from the second medium. Separation of the background support removes nonspecific background noise from the medium.

As illustrated, background capture is effected upon beads. However, those skilled in the art will recognize that the initial purification of the target-first and second probe complex from the clinical sample, removes all or most solid debris allowing background capture on filter or membrane supports through which the second medium can be flushed.

From Station 8, the purified medium containing the target-probe complex with reduced background is conveyed to Station 9. At Station 9, a third support, depicted as a membrane or filter, is brought into contact with the second medium which is brought to hybridization temperatures by a heating element. The third support includes first antiligand moieties which bind to the first ligand moieties of the first probe, or if an amplification product is generated in previous steps, to a first ligand moiety of a third probe directed to the amplification product. Thus, if the first ligand moiety of the first probe is of a homopolymer of deoxyadenosine (dA), the third support may include homopolymer of deoxythymidine (dT). As illustrated, the third support includes filters or membranes through which the second medium can be flushed; however, beads or particles may also be used. The third support serves to further concentrate the target-first and

second probe complex and permits further reduction of background and interfering materials which do not specifically bind to the third support. Moving to Station 10. the third support concentrates the target-first and second probe complex allowing detection of label moieties carried upon the second probe.

The present invention is further described in the following typical procedures and experimental examples which exemplify features of the preferred embodiment.

I. PROCEDURES

A. Materials

All reagents were of analytical grade or better. Magnetic beads marketed under the trademark BIO-MAG containing functional amino groups were obtained from Advanced Magnetics. Inc. of Cambridge. Mass.

In the present example. all labeled nucleotides were obtained from New England Nuclear. The enzyme terminal deoxynucleotidyl transferase (TDT) was obtained from Life Sciences. Inc.. St. Petersburg. Fla. The oligonucleotide pdT_{10} was obtained from Pharmacia PL Biochemicals.

B. Synthesis of Probes

The following sets forth typical protocols and methods. Referring now to FIG. 8. two probes were constructed to the sense strand of the enterotoxin gene elt Al of *Escherichia coli*, in accordance with the constructional map, FIG. 8, of Spicer. E. K. and J. A. Noble, 1982. *J. of Biological Chem.* 257. 55716–55751.

One set of probes was synthesized beginning at position 483 of the gene sequence and extending onward 30 nucleotides in length. hereinafter referred to as the A483 probe. A second probe was synthesized beginning at position 532 in the gene sequence and extending 30 nucleotides in length. hereinafter referred to as the A532 probe. A third probe was synthesized beginning at position 726 in the gone sequence and extending 39 nucleotides in length. hereinafter referred to as the A726 probe. The specific base sequences (5' to 3') are set forth in Table 1 below:

TABLE I

Probe	Sequence
A483	AGA CCG GTA TTA CAG AAA TCT GAA TAT AGC
A532	AGA TTA GCA GGT TTC CCA CCG GAT CAC CAA
A726	GTC AGA GGT TGA CAT ATA TAA CAG AAT TCG GGG GGG GGG

The probes were synthesized by methods available in the art. The numbering system is adapted from the 768 nucleotide sequence available through Intelligenetics sequence bank ECO ELT Al.

Of the ten G resicues at the 3 prime end of probe A726. three guanine bases towards the 5' end are capable of binding to three complementary cytosine bases of the tox gene. Stretches of three cytosines are common in DNA. The ten guanine bases form a ligand capable of binding to a poly C antiligand carried upon a support such as oligo dC-cellulose. However. seven guanine bases will not form a stable association with a support at 37° C., particularly if the probe is bound to target due to steric hindrance and the size of the target-probe complex. Probe A726 was modified by the random addition of approximately three residues of ^{32}P-dC and ^{32}P-dG to its 3' end with terminal transferase.

Those skilled in the art will recognize that other probes can be readily synthesized to other target molecules.

C. Preparation

The target in Example Nos. 1. 2 and 3 is the enterotoxin gene elt Al. The enterotoxin gene elt Al is carried as part of the plasmid EWD-299 obtained from Stanford University.

In Example No. 1. enterotoxigenic bacteria were grown to log-phase in Luria broth. The enterotoxigenic bacteria were lysed and the plasmid EWD-299 isolated. The plasmid EWD-299 was further digested with the restriction enzymes Xba 1 and Hind III. A fragment of 475 base length was used as target and purified by electro-elution from a 1 percent agarose gel. In order to follow the efficiency of capture steps. the fragment was 5' end labeled with ^{32}P-ATP with the enzyme polynucleotide kinase following manufacturer's instructions.

In Example Nos. 2 and 3. the enterotoxigenic bacteria and wild type nonenterotoxigenic *E. coli* JM83 were separately grown to log phase. The wild type *E. coli* serves as a control. Separate extracts of enterotoxigenic bacteria and wild type bacteria were prepared by substantially solubilizing the cells in chaotropic solutions. Thus. the bacteria cultures, in Luria broth. were added to solid guanidinium thiocyanate (GuSCN) to a concentration of 5M GuSCN. Tris-HCl to a concentration of 0.3M. and EDTA (pH7) to a concentration of 0.1M. The chaotropic-bacterial solutions were then heated to 100° C. for five minutes and cooled. The resultant enterotoxigenic bacteria extract was serially diluted with wild type nonenterotoxigenic bacteria extract. The concentration of tox plasmids per cell and the cell number in the extracts were measured by conventional techniques. The original extracts solubilized in GuSCN contained approximately 10^9 enterotoxigenic *E. coli* per ml and 100 plasmids/cell.

D. Synthesis of Beads

Retrievable supports were prepared from magnetic beads. Other retrievable supports include particles. fibers. polystyrene beads or other items capable of physical separation from a medium. Magnetic beads were synical separation from a medium. Magnetic beads were synthesized with an adduct of deoxythymidine of ten base length to allow the beads to associate with probes tailed with deoxyadenosine in a readily reversible manner.

Thus, 100 ml of beads having amine functional groups such as BIO-MAG (M4100) beads were washed four times with 20 mM sodium phosphate (pH 6.7) in four 275 ml T-flasks. The beads were then washed with 1% glutaraldehyde in 20 mM sodium phosphate. Next. the beads were reacted in 100 ml of 10 percent glutaraldehyde in 20 mM sodium phosphate (pH 6.7) for three hours at room temperature. The beads were then washed extensively with 20 mM sodium phosphate (pH 6.7) and then washed once with 20 mM phosphate (pH 7.6).

Separately, a purified ethylene diamine (EDA) adduct of pdT_{10} (EDA-dT_{10}) was prepared in accordance with Chu. B. C. F.. G. M. Wahl. and L. E. Orgel; Nucleic Acid Res. 11,

6513–6529 (1983) incorporated by reference herein. The concentration of EDA-dT_{10} was adjusted to 1 OD/ml in 20 mM phosphate (pH 7.6).

The EDA-dT_{10} was combined with the magnetic beads to allow the EDA-dT_{10} to react with the free aldehyde groups of the beads. The mixture of EDA-dT_{10} and beads was divided into a plurality of 50 ml polypropylene tubes. The tubes containing the reaction mixture and beads were placed in a tube rotator and agitated overnight at room temperature.

Next, the beads were washed five times to remove non-covalently bound EDA-dT_{10} with a wash solution of sterile 20 mM phosphate (pH 6.7) in large 275 ml T-flasks and diluted to 200 ml with the wash solution.

For storage, beads can be maintained for months in a buffer of 20 mM phosphate, to which is added sodium azide to 0.1% and SDS to 0.1%. Bead preparations are stored at 4° C. protected from light.

The beads were then prehybridized to block nonspecific binding sites in a buffer, hereafter referred to as "prehybridization buffer", of 0.75M sodium phosphate (pH 6.8), 0.5% sodium lauroyl sarcosine, 10 micrograms/ml *E. coli* DNA, 0.5 milligram per milliliter mg/ml bovine serum albumin (BSA) (Nuclease-free) and 5 mM ethylenediaminetetraacetic acid) (EDTA). Before applying the probes and beads to target capture procedures, two prehybridizations of the beads were performed. The prehybridization procedure included placing the beads in ten volumes prehybridization buffer.

The first prehybridization procedure was performed with agitation at 60° C. The second prehybridization procedure was performed at room temperature with swirling. A 0.1 percent isoamyl alcohol solution was added to the solutions as a defoamant.

The binding capacity of dT_{10}-derivatized beads was measured by the following procedure. In separate vessels, dT_{50} and dA_{50} were 5' end labeled with ^{32}P-dT and ^{32}P-dA respectively to a specific activity (Sa) of about 10^6 dpm/microgram. Next, the Sa was accurately measured for a known quantity of reacted dT_{50} by trichloroacetic acid precipitation.

Next, 5 μg of ^{32}P-dA_{50} and 5 μg of ^{32}P-dT_{50}, having substantially identical Sas of between 100.000–200.000 dpm/mg, were separately added to tubes containing prehybridization buffer and brought to a volume of 1 ml.

A known sample volume of prehybridized beads was placed into four tubes. Two of the four tubes each receive 0.5 ml of the ^{32}P-dA_{50} mixture and the remaining two tubes receive 0.5 ml of the ^{32}P-dT_{50} mixture. All four solutions are brought to hybridization conditions for five minutes. The beads are thereafter immobilized and washed. The activities of the solutions are then monitored. The total binding capacity, C, for a quantity of bead preparation measured in micrograms is set forth below:

$$C=V(A-T)X$$

In the above equation X is the specific activity of ^{32}P-dT_{50} in cpm/mg, V is the volume ratio of total volume to sample volume, A is the average activity of the beads suspended in ^{32}P-dA solutions in cpm, and T is the average activity of the beads suspended in ^{32}P-dT solutions in cpm.

Those skilled in the art will recognize that other beads, particles, filaments, and the like can be formulated with other nucleotide combinations or homopolymers. For example, polyA-derivized beads were produced by substituting (for the purified EDA adduct of dT_{10}) a solution containing 100 mg poly A (mw>100,000) in 50 ml of 20 mM sodium phosphate (pH7.6).

E. Target Capture Procedures

Bead preparations were used to capture target polynucleotides. The following sets forth a typical experimental target capture protocol demonstrating retrievable supports and reversible captures for purposes of illustration, without limitation, the procedure will be discussed using a first probe A483 and a second probe A532. The first probe, A483, was randomly 3' end labeled with ^{32}P-dCTP and ^{32}P-dGTP to a specific radioactivity of about 10^{10} dpm/mg. The second probe, A532, was trailed with about 70 unlabeled dA residues by the enzyme terminal transferase.

First, 200 μg/ml of labeled probe A483 and 400 μg/ml of tailed probe A532 were mixed with varying amounts of a heat-denatured 475 me Xba 1-HIND III restriction fragment of the enterotoxin gene at 65° C. for 15 minutes in 1.4M sodium chloride.

Next, target capture was initiated by contracting the medium containing the target and probe moieties with an aliquot of dT_{10}-magnetic beads having 3 micrograms/ml of dA_{50} binding capacity following prehybridization procedures to reduce nonspecific binding to the magnetic bead. The magnetic bead and the probe-target complex was incubated at room temperature in 0.1 ml prehybridization buffer in 5 ml polypropylene tubes for two to five minutes.

The tubes were placed into a Corning tube magnetic separator. The Corning tube magnetic separator upon activation imposes a magnetic field through the polyproplyene tubes which immobilizes the magnetic beads on the inner walls of the tubes. During the time that the magnetic beads are immobilized on the side walls of the polypropylene tubes, the original medium was removed and discarded.

While immobilized, the beads were washed three times with 0.6 ml of prehybridization buffer containing isoamyl alcohol as a defoamant. Following the addition of the prehybridization buffer, the beads were resuspended by removing the tubes from the magnetic field and by subjecting the medium to vigorous vortexing.

Next, the magnetic field was reapplied to immobilize the beads allowing the prehybridization buffer to be removed and discarded. The cycle of adding the prehybridization buffer, resuspending the beads, immobilizing the beads, and discarding the prehybridization buffer was repeated twice. Target-probe complexes held on the beads are available for further processing including additional steps of detection, background capture or further cycles of target capture.

A preferred target capture procedure includes release of the target-probe complex and recapture on a second support. Preferably the support is chemically distinct from the first support.

Release of the target-probe complex is effected in the following typical protocol. After the removal of the last prehybridization buffer, prehybridization buffer was added to the tube containing the beads. The beads were incubated with agitation at 60° C. for one–two minutes to release the probe-target complexes from the bead. The magnetic separator was again activated with the temperature at 60° C. and the eluate, containing free target-probe complexes, is removed from the tube. The eluate can be recaptured on additional retrievable supports or subjected to final capture on conventional supports. It will be recognized by those skilled in the art that the capture and release of the target probe complex from retrievable supports such as the magnetic beads of the present example can be repeated as often as desired to reduce hybridization backgrounds.

Final capture of the probe-target complex was typically performed on nitrocellulose filters or nylon membranes containing nonspecifically bound or covalently bound dT-3000. Thus, the target-probe complexes carried upon the magnetic beads were released from the magnetic beads by heating the beads to 60° C. in prehybridization buffer for two minutes. The beads were immobilized and the eluate removed and passed through a 0.2 micron acrodisc (Gelman) to remove magnetic fines. The nitrocellulose filter containing dT-3000 selected, bound, and captured the dA tail on the unlabeled probes.

The use of a chemically different solid support for the final capture of the target-probe complex avoids binding background molecules which may have a high affinity for previously used supports. By way of illustration, it is possible for lower level contaminants with a natural high affinity for a particular support to repeatedly bind and elute with a support along with probe-target complexes. Such low level contaminants cannot be diluted out by repeated use of a retrievable support of the same composition as completely as by exposing them to supports of very different compositions. Low level contaminants can also be lowered by utilizing chemically distinct means to release the target-probe complexes from supports and recapture.

F. Background Capture Procedures

Background capture procedures permit the selective reduction of background noise permitting the detection of signal indicative of the presence of target. Background capture can be applied in a single probe system or in systems using more than two probes. For example, in background capture procedures featuring a single probe, the probe includes a label moiety and a ligand. The probe is capable of binding to a target and the ligand is capable of forming a stable bond to a support only when the probe is unbound to target.

Similarly, by way of example, background capture procedures featuring multiple probes in conjunction with target capture include two probes. A first target capture probe, having an unlabeled ligand capable of binding to a first support is used to capture the target and a second background capture probe, having a label moiety capable of detection includes a second ligand capable of binding to a second background support. Background capture is a valuable supplement to target capture for enhancing the signal to noise data of an assay.

The following sets forth a typical background capture protocol using a first target capture probe A532 and a second background capture probe A726 and a target enterotoxin gene elt A1. Those skilled in the art will recognize that the probes used for demonstration purposes are merely a matter of choice. Other probes could be used also.

The probe A532 was tailed with approximately 100 dA residues capable of reversibly binding to dT_{10} covalently linked magnetic beads for initial target capture and dT_{3000} nonspecifically bound to nitrocellulose for a final target capture. The probe A726 was end labeled with the random addition of approximately three residues of ^{32}P-dC and ^{32}P-dG to the 3' end with terminal transferase. The probe A726 is capable of binding to dC-cellulose when the probe is not hybridized to target.

A solution containing the target-first and second-probe-complex and potentially containing unbound second probe is mixed with dC-cellulose and the temperature of the mixture maintained at 37° C. The temperature, 37° C., is higher than the dissociation temperature of dG_7 with oligo dC, preventing binding of the target-first and second-probe-complex to the dC-cellulose. The temperature is also lower than the dissociation temperature of dG_{10} with oligo dC to promote binding of unbound second probe having a dG tail to the dC-cellulose. Additional, the target-first and second probe complex is sterically hindered to a greater degree in its approach to the dC-cellulose support than unbound second probe. The dC-cellulose containing the second probe A726 is removed by centrifugation, however, those skilled in the art will appreciate that other methods such as filtration may be used as well. The remaining eluate contains target-first and second probe complexes and a reduced concentration of unbound labeled second probe A726.

G. EXAMPLES

Individual skilled in the art will recognize that the typical protocols for retrievable support preparation, probe preparation, target capture and background capture are capable of modification to suit special needs and purposes. The following examples incorporate the typical procedures outlined above unless otherwise noted.

Example 1

Target Capture and Assay Using Magnetic Bead

A target capture assay was performed with two probes and a magnetic bead retrievable support. The target included the Xba 1-Hind III fragment of the enterotoxigenic gene elt A1. A first probe included an A532 thirtimer oligonucleotide probe which was tailed with 130 unlabeled dA residues capable fo binding to the dT_{10} residues of the magnetic beads support. A second probe included an A483 thirtimer oligonucleotide probe capable of binding to the same target 20 nucleotides downstream from the site of hybridization of the first probe. The second probe was labeled by tailing the thirtimer oligonucleotide with ^{32}P-dCTP and ^{32}P-dGTP to a specific radioacitivity of 10^{10} DPM/microgram.

The tailed first probe and the labeled second probe were incubated at 65° C. for 15 minutes in 1.4M sodium chloride with various quantities of heat denatured 475 mer restriction fragments of the tox gene. As a nonspecific binding background control, the tailed first probe and labeled second probe were incubated in identical solutions in the absence of any target. As specific binding controls, two additional reaction mixtures were formed. One reaction mixture included the tailed first probe and the unlabeled second probe incubated with four micrograms of denatured *E. coli* DNA, and a second reaction mixture of the tailed first probe and the labeled second probe incubated in ten micrograms of denatured human DNA in identical reaction mixtures without any target DNA.

After a 15 minute hybridization period, the samples were incubated for five minutes with dT-derivatized magnetic beads in 0.7 milliliters of 0.75 molar phosphate buffer (pH 6.8). The beads were magnetically immobilized and washed extensively as described previously. The target-probe complex was eluted from the beads at 60° C. in 0.6 milliliters of 0.20 molar phosphate buffer (pH 6.8). The first set of beads was separated from the eluate and the target probe complex. A second group of magnetic beads was added to the eluate and brought to binding conditions to capture the target and probe complex again. The second set of beads was washed and the target again eluted from the beads and the beads separated from the eluate.

A third set of beads was added to the eluate containing the target-probe complex and placed under binding conditions to allow the beads to once again capture the target-probe complex. The beads were then washed extensively and the target eluted from the beads as previously described. The beads were then separated from the eluate and the eluate

passed through dT_{3000}-nylon into two millimeter square slots, capturing the target-probe complex.

The dT_{3000} nylon membrane was prepared in which 2 μg dT_{3000} was covalently bound to nylon using a hybri-slot apparatus (Bethesda Research Laboratory). Briefly, dT_{3000} (Life Sciences) was dotted directly onto a nylon membrane such as Gene-Screen™ (New England Nuclear) in a salt-free Tris buffer. The membrane was dried at room temperature for 10 minutes, and then dried under an infrared lamp for an additional 10 minutes before cooling back to room temperature for another 10 minutes. The filter apparatus containing the nylon membrane was inverted on a uv-transilluminator (Fotodyne) and exposed to uv light for two minutes at 40 uW/cm^2 to cross-link the dT_{3000} to the filter.

The dT_{3000} membrane was prehybridized by sequentially passing the following solutions through the membrane:

(1) 1% SDS;

(2) 0.5 mg/ml BSA in 0.5% SDS: and, finally,

(3) prehybridization buffer

The dT_{3000}-nylon potentially containing the target-probe complex was washed with 0.2 molar sodium phosphate and 5 millimolar EDTA. The nylon support was monitored overnight by audioradiography for the presence of the ^{32}P label moieties of the second probe. Following audioradiography, the bands were cut out of the filter and counted in base scintillation fluid. The counts were 2100 and 1400 counts per minute in the solution containing three femtomoles (10^{-15} moles) of a restriction fragment containing the tox gene. Samples containing 30 attomoles (10^{-18} moles) of the restriction fragment containing the tox gene produced a count of 62 counts per minute.

A third sample containing no DNA produced seven counts per minute. A fourth sample containing ten micrograms of heat denatured human DNA produced 0 counts per minute. A fifth solution containing 4 micrograms of heat denatured *E. coli* DNA produced 7 counts per minute. The absoluted sensitivity of the protocol was estimated to be 10^{-18} of tox gene. The overall efficiency of the recovery of labeled target-probe complex was estimated to be 1 to 2 percent of the input. The assay demonstrated good specificity. There is no more labeled probe in the samples containing human DNA or *E. coli* DNA than in the sample containing no DNA at all. Repetition of the experimental protocol has produced overall efficiency of capture of the target of almost 5 percent. The procedures reduced background from an initial level of 10^{11} molecules of the labeled unhybridized probes to about 10^4 moles. The reduction and background represents a 7 log improvement which more than adequately compensates for the reduction and efficiency of capture.

Example 2

The present example features target capture with background capture. Target and background capture was effected using an unlabeled first target capture probe, A532 as described in target capture, and a second labeled background capture probe A726.

First, 160 ng/ml dA-tailed A532 and 40 ng/ml ^{32}P-labeled probe A726 were combined to form a probe mix. The probe mix was added to 5 μl of bacterial extract containing various amounts of enterotoxigenic gene. The extract-probe mix was incubated at 22° C. for 15 minutes.

After a fifteen minute hybridization period, the samples were diluted with ten volumes of prehybridization buffer incubated for five minutes with dT-derived magnetic beads in 0.7 ml of 0.75M phosphate buffer (pH 6.8) to effect target capture. The beads were magnetically immobilized and washed extensively. The target-first and second probe complex was eluted from the first support as previously described and the first solid support removed.

Next, the eluate containing the target-first and second-probe-complex and potentially containing unbound second probe was mixed with dC-cellulose and the temperature of the mixture maintained at 37° C. The temperature 37° C. is higher than the dissociation temperature of dG_7 with oligo dC to prevent binding of the target-first and second-probe-complex to the dC-cellulose. The temperature was also maintained lower than the dissociation temperature of dG_{10} with oligo dC to promote binding of unbound second probe having a dG_{10} tail to the dC-cellulose. The target-first and second probe complex is sterically hindered to a greater degree in its approach to the dC-cellulose support than unbound second probe. The dC-cellulose was removed by centrifugation, however, those skilled in the art will appreciate that other methods such as filtration may be used as well.

The remaining eluate was passed through a 0.2 micron acrodisc (Gelman) to remove magnetic and cellulose fines. Then, the eluate was passed through nitrocellulose filters containing dT_{3000} at 22° C. The nitrocellulose effected final target capture.

Table 2 sets forth below the application of background capture:

TABLE 2

Step	Signal (CPM)	Noise (CPM)
First Experiment		
Before Target Capture	(unknown)	200,000
After Target Capture	1058	231
After Background Capture	495	25
After Filtration	395	<1
Second Experiment		
Before Target Capture	(unknown)	400,000
After Target Capture	1588	642
After Background Capture	1084	69
(Filtration step was not performed)		

The removal of noise to less than 1 cpm allows the detection of very small quantities of target within a sample. As little as 10^{-18} moles of target have been detected which is within the range necessary for clinical applications.

One round of target capture removed about 3 logs of background. One round of background capture removed 1 log of background not already removed by the primary target capture. Final target capture by filtration (a second round of target capture) removed 2 logs of background not removed by either of the first two steps. Target and background capture methods work independently to reduce backgrounds by about 6 logs in this example. Background capture appears to work better when applied after a first target capture. Apparently, background capture is much more sensitive to impurities in the sample than target capture.

The combination of background capture following target capture produces a greater benefit than either applied alone.

Although the foregoing examples recite radioactive label moieties, it is expected that the present procedure would have its greatest impact on assay procedures utilizing non-radioactive label moieties. In particular, the present invention would be applicable to luminescent label moieties including fluorescent and chemiluminescent agents. Suitable fluorescent labels include, by way example without limitation, fluoroscein, pyrene, acridine, sulforhodamine,

eosin, erythrosin, and derivatives thereof. Suitable chemiluminescent agents include, by way of example without limitation, microperoxidase, luminol, isoluminol, glucose oxidase, acridinium esters and derivatives thereof.

Example 3

The following example features nonradioactive label moieties and multiple rounds of target capture from spiked biological media. The spiked biological media resembles samples which would be obtained clinically in a medical setting.

Cell extracts of enterotoxigenic *E. coli* and wild type *E. coli* were prepared as previously described. To measure the sensitivity of the detection of tox genes in an environment analogous to a clinical setting, extract containing toxigenic bacteria was diluted with the extract containing the wild type *E. coli* as previously described.

The following materials were obtained from anonymous donors: human stool sample, cow's milk, human saliva, human phlegm, human whole blood, human serum, human urine and human semen. Clinical-type samples were solubilized over a time period of ten minutes. The stool sample, due to its solid nature, was solubilized in a solution of 5M GuSCN, 0.3M Tris-HCl (pH 7.4), 0.1M EDTA (pH 7), 1% betamercaptoethanol. Following solubilization, aliquots of the sample were made and each aliquot was spiked with a known quantity of either toxigenic *E. coli* or wild type *E. coli*. The mixture was then passed through a crude filtration (Biorad Econocolumn) and heated to 100° C. for five minutes.

The remainder of the samples were more liquid in nature and were handled differently than stool. Liquid samples were added to solid GuSCN to make the final concentration 5M. The solid GuSCN also contained sufficient Tris-HCl, EDTA, and betamercaptoethanol to make the final concentrations the same as in the stool example. Next, aliquots of the samples were made and each aliquot was spiked with a known amount of toxigenic *E. coli* or wild type *E. coli*. The mixture was passed through a crude filtration (Biorad Econocolumn and heated to 100° C. for five minutes.

The preparation of probes in Example 3 differs from previous examples. A first capture probe was generated with the plasmid pBR322. The plasmid was restricted with Hha I and Hae III and plasmid fragments were tailed with about 100 dA residues with terminal transferase. The target plasmid contains extensive homology with pBR322 (Spicer and Noble, *J. Biol.* 257: 5716–21). Thus, first capture probes were generated from multiple fragments of both strands of the plasmid pBR322 in relatively large quantities.

A second label probe was made to combine specifically to the target enterotoxin gene. The second label probe was generated from an EcoRI-Hind III restriction fragment of the elt A1 gene cloned into bacteriophage M13mp18. The *E. coli* HB101 was infected with the bacteriophage and grown to midlog phase. The *E. coli* were harvested, and the bacteriophage were isolated. Bacteriophage was nick-translated with biotinylated dCTP (Enzo-Biochemicals) using a stock nick-translation kit available from Bethesda Research Laboratories. Approximately five percent of the nucleotides were replaced with biotinyl nucleotides to form a biotin-labeled second probe.

A probe mix was made by combining 8 μg/ml of the second M13-tox probe with 4 μg/ml of the first dA-tailed first probe in 20 mM Tris-HCl (pH 7.4) and 2 mM EDTA. The probe mix was heated to 100° C. for ten minutes to denature the probes.

One volume of the probe mix was mixed with one volume of sample of the dilution series to form a hybridization mixture. The hybridization mixture was maintained under hybridization conditions at 57° C. for fifteen minutes. The hybridization mixtures were subsequently diluted with ten volumes of blocking buffer 0.75M sodium phosphate, pH 6.8, 0.5% sodium lauryl sarcosine, 10 mg/ml *E. coli* DNA, 0.5 mg/ml bovine serum albumin (BSA-nuclease free) and 5 mM EDTA). To the hybridization mixture were added dT_{10} derivized magnetic beads prepared as previously described. Hydridization conditions were maintained approximately one minute at 22° C. The beads were then separated from the hybridization mixture by magnetically immobilizing the beads. The beads were washed twice during a fifteen minute time interval to remove impurities in the biological specimen and unhybridized biotin labeled second probe.

Next, in a time period of approximately one minute, the first and second probe-target complex was eluated from the magnetic beads at 65° C. in blocking buffer. The eluate and the first beads were separated.

In a time period of approximately seven minutes, the first and second probe-target complex was releasibly bound to a second set of beads and again released. A second set of dT_{10} derivized beads were then added to the eluate and hybridization conditions maintained for approximately one minute at 22° C. The beads were then washed and resuspended in blocking buffer. The bead blocking buffer mixture was then brought to 65° C. to release the first and second probe-target complex.

Over a time period of five minutes, final capture of the first and second probe-target complex on nitrocellulose was effected. The eluate from the second beads was filtered through a Gelman acrodisc (0.2 micron). The eluate containing the first and second probe-target complex was then passed through a dT_{3000} nitrocellulose filter (prehybridized with blocking buffer) at 22° C.

In a time period of approximately thirty minutes the filter was further processed to detect the biotin labels of the second probe. Buffer compositions used in detection are identified below in Table 3.

TABLE 3

Detection Buffers

Buffer Number	Composition
1	1 M NaCl, 0.1 M Tris-HCl (pH 7.4), 5 mM $MgCl_2$, 0.1% Tween-20
1a	No. 1 with 5 mg/ml BSA, 10 micrograms/ml *E. coli* DNA
2	No. 1 with 5% BSA, 0.5% Tween-20
3	0.1 M NaCl, 0.1 M Tris-HCl (pH 9.5), 50 mM $MgCl_2$

First, the filter carrying the first and second probe-target complex, was incubated for approximately five minutes in detection buffer No. 2. Next, the filter was incubated for five minutes in a 1:200 dilution of streptavidin-alkaline phosphatase (Bethesda Research Laboratories) in detection buffer No. 1a. Thereafter, the filter was washed three times in one minute in detection buffer No. 1 and then washed twice in one minute in detection buffer No. 3.

Next, 5-Bromo-4-chloro-3-indolyl phosphate (BCIP) and nitroblue tetrazolium (NBT) (Kierkegaard and Perry) were diluted twelve times in detection buffer No. 3, and filtered through a 0.2 micron acrodisc. The diluted BCIP and NBT

solution was added to the filter and color allowed to develop for fifteen minutes at 37° C.

Next, the filter was incubated in 50 mM Tris-HCl (pH 7.4) and 10 mM EDTA for one minute to stop the reaction. Sensitivity was determined visually on the filter or by densitometric scanning on a CS 930 (Shimadzu Scientific).

The steps in the present method are outlined below in Table 4.

TABLE 4

Elapsed Time

Step Number	Time Required (min.)	Cumulative Timed (min.)
1. Dissolution of biological sample; denaturation of DNA	10	10
2. Add labeled and unlabeled probes; hybridize in solution at 57° C.	15	25
3. Capture probe-target complex on magnetic beads	1	26
4. Wash magnetic beads to remove impurities in the biological specimen and hybridization backgrounds	15	41
5. Elute the probe-target complex	1	42
6. Repeat steps 3–5 on a second set of beads (except abbreviate the washes)	7	49
7. Bind the probe-target complex to dT_{3000}-nitrocellulose	5	54
8. Incubate filter in blocking buffer	5	59
9. Bind streptavidin-alkaline phosphatase	5	64
10. Wash	5	69
11. Add dyes to detect enzyme	15	84
12. Quench reaction	1	85

Although Table 4 set forth an example wherein the elapsed time is just over one hour, the procedure is capable of modification and can be performed in shorter times. Nonradioactive probe assays of comparable sensitivity may require twelve hours to several days and require extensive sample preparation.

The sensitivity of the present assay is set forth in Table 5 below:

TABLE 5

Sensitivity Level

Biological Specimen	Concentration in the Hybridization Mixture	Number of Bacteria
bacterial extract alone		1500
human stool	2.5% (w/v)	2000
cow's milk	12.5% (v/v)	3000
human saliva	12.5% (v/v)	3000
human urine	12.5% (v/v)	9000
human semen	2.5% (v/v)	9000
human blood	12.5% (v/v)	9000
human serum	12.5% (v/v)	9000
human phlegm	12.5% (v/v)	9000

Further, the present procedures are capable of further modifications to improve sensitivities. For example, a combination of thermal elution and chemical elution in multiple captured release cycles produces a signal to noise ratio five times better than single forms of elution, either multiple thermal elutions alone or multiple chemical elutions alone.

Applying the same releasing or elution procedure tends to release the same background from the support. However, applying different releasing conditions tends to retain background on the support that would otherwise be eluted. It is unlikely that background will behave identically to target under two physically or chemically distinct conditions.

A typical chemical elution of target-probe complexes on magnetic beads includes bringing beads in contact with 3 M GuSCN for one minute at room temperature. Examples of thermal elutions have been described previously.

The ability to detect bacteria would also be improved by directing probes to ribosomal RNA sequences. Ribosomal RNA sequences present to thousand fold increase in target per cell as compared to genomic DNA and clinically significant plasmid DNA.

The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by non-specific replication using standard enzymes (polymerases and/or transcriptases). After replication, the amplified nucleic acid can be reacted as above with capture probe, reporter probe, and capture beads to purify and then detect the amplified sequences.

In addition, where amplification is employed following purification of the target nucleic acids as described above, the amplified nucleic acids can be detected according to other, conventional methods not employing the capture probe, reporter probe, and capture beads described above, i.e., detection can be carried out in solution or on a support as in standard detection techniques.

Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ non-specific enzymes or primers (i.e., enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence). Although any background, non-target, nucleic acids are replicated along with target, this is not a problem because most of the background nucleic acids have been removed in the course of the capture process. Thus no specially tailored primers are needed for each test, and the same standard amplification reagents can be used, regardless of the targets.

The following are examples of the method.

Example 4

The following example illustrates the use of RNA polymerase to amplify target DNA captured by a method which is a variation of the capture method discussed above.

Referring to FIG. 4, target DNA of a sample is first reduced in size by shearing or by limited nuclease digestion, according to standard methods. A recA protein coated capture probe is then added to the digested target DNA (*Proc. Natl. Acid. Sci.* U.S.A. (1986) 83:9591) The recA protein coated probe contains a nucleic acid sequence (a) that is homologous to a first target (a^1) sequence of the target DNA, as well as a homopolymer sequence homologous to a nucleic acid sequence on a capture bead. This capture bead is then added to the mixture to isolate and purify the target nucleic acid, as described above.

The capture DNA is amplified by treatment of the mixture with *E. coli* RNA polymerase lacking sigma subunit, i.e., core enzyme; *E. coli* RNA polymerase is described by R. Burgess in *RNA Polymerase*, Cold Spring harbor press, pp. 69–100, and can be purchased from New England Biolabs, Beverly, Mass. The sigma subunit is removed according to the procedure described in J. Biol. Chem. (1969) 244:2169 and Nature (1969) =221=:43. Other phage or bacterial RNA polymerases that lack transcriptional specificity can also be

used. Core enzyme is added together with nucleotide triphosphates and a low salt transcription buffer such as described in Eur. J. Biochem. (1976) 65:387 and Eur. J. Biochem (1977) 74. 1107.

A suitable nucleotide triphosphate/transcription buffer solution has the following composition:

0 to 50 mM NaCl or KCl

25 mM Tris HCl pH 7.9 buffer

10 mM $MgCl_2$

0.1 mM EDTA

0.1 mM dithiothreital

0.5 mg/ml BSA

0.15 mM UTP. GTP. CTP. ATP

The resulting non-specific transcription of the target DNA produces many RNA transcripts of the target DNA which are then captured using a capture probe containing a sequence (b^1) homologous to a sequence (b) of the RNA transcripts. A reporter probe containing a sequence (c^2) homologous to another sequence (c) of the RNA transcript is then used for detection.

Example 5

In this example both non-specific replication of target DNA and transcription of that DNA are used to amplify capture target DNA.

Referring to FIG. 5. denatured sample DNA is captured as described above and the enzyme DNA polymerase (for example. Klenow fragment; Dur. J. Biochem. (1974) 45:623 available from New England Biclabs). random oligohexamer primers (i.e.. Hexamers prepared to contain randomly selected bases at each nucleotide position in the hexamer) and deoxynucleotide triphosphates are added in appropriate buffers to cause replication of target DNA to form additional double stranded DNA. Suitable oligohexamer primers are available under catalog No. 27-2166 from Pharmacia. Inc. Piscotaway, N.J. A suitable deoxynucleotide triphosphate/buffer solution has the following composition:

66 mM glycine-NaOH buffer. pH 9.2

6 mM $MgCl_2$

1 mM 1-mercaptoethonal

30 mM each d CTP. d GTP. d TTP. d ATP

Because the primers are random. some will. simple as a matter of statistics. bind to and cause replication of sample sequences. no matter what those sequences are. (Alternatively. the double stranded DNA can be formed by synthesis starting from capture probe a.) RNA polymerase lacking sigma subunit is then added along with nucleotide triphosphates and low salt transcription buffer. Transcription from the target DNA (which has been increase d in number) produces many RNA copies of this DNA. The RNA transcripts are then captured and detected as in example 4.

Example 6

In this example target DNA is replicated using DNA polymerase.

Referring to FIG. 5. sample DNA is denatured. reduced in size and captured as described in examples 4 and 5. DNA polymerase. for example. Klenow fragment. and deoxynucleotide triphosphates are added in appropriate buffer with random hexamer oligonucleotides to bring about non-specific double-stranded DNA syntheses. The in vitro synthesized DNA product is then made single stranded by heat treatment (e.g.. 100° C. for three minutes). or its equivalent. and additional DNA polymerase is then added to replace that rendered inactive by the heat treatment. Further in vitro DNA replication then is allowed to occur. The heat treatment and polymerization reactions are repeated about 10 times to produce an approximately 1.000-fold increase in the level of target DNA. The replicated DNA is denatured in vitro using heat or alkali and then captured and detected as described previously.

Example 7

In this example. rRNA or RNA transcribed from target DNA is purified using a capture probe. described above. The hybrid duplex is then denatured and single stranded nucleic acids are then replicated non-specifically using Qβ replicase (methods in Enzymology (1979) 60:628. This replicase replicated both messenger RNA and ribosomal RNA non-specifically under the conditions described by Blumental. Proc. Natl. Acad. Sci. U.S.A. 77:2601. 1908. Because the replication product is a template for the enzyme. the RNA is replicated exponentially.

While preferred embodiments have been illustrated and described. it is understood that the present invention is capable of variation and modification and. therefore. should not be limited to the precise details set forth. but should include such changes and alterations that fall within the purview of the following claims.

We claim:

1. A method for amplifying a target polynucleotide contained in a sample comprising the steps of:

(a) contacting the sample with a first support which binds to the target polynucleotide;

(b) substantially separating the support and bound target polynucleotide from the sample; and

(c) amplifying the target polynucleotide.

2. The method of claim 1 wherein the first support is retrievable.

3. The method of claim 1 wherein the first support includes a probe which binds with the target polynucleotide.

4. The method of claim 1 wherein the target polynucleotide is amplified with a polymerase.

5. The method of claim 4 wherein the polymerase is a DNA polymerase, an RNA polymerase, a transcriptase or Qβ replicase.

6. The method of claim 4 wherein the target polynucleotide is a DNA polynucleotide and the polymerase is a DNA polymerase.

7. A method for detecting a target polynucleotide contained in a sample comprising the steps of:

(a) contacting the sample with a first support which binds to the target polynucleotide;

(b) substantially separating the first support and bound target polynucleotide from the sample;

(c) amplifying the target polynucleotide; and

(d) detecting the presence of the amplified target polynucleotide.

8. The method of claim 7 wherein the first support is retrievable.

9. The method of claim 8 wherein the first support includes a probe which binds with the target polynucleotide.

10. The method of claim 7 wherein the target polynucleotide is amplified with a polymerase.

11. The method of claim 10 wherein the polymerase is a DNA polymerase. an RNA polymerase. a transcriptase or Qβ replicase.

12. The method of claim 11 wherein the target polynucleotide is a DNA polynucleotide and the polymerase is a DNA polymerase.

13. The method of claim 7 wherein the amplified target polynucleotide is contacted with a label.

14. The method of claim 7 wherein the amplified target polynucleotide is contacted with a labeled probe.

15. The method of claim 7 wherein the amplified target polynucleotide is contacted with a second support which binds to the amplified target polynucleotide.

16. The method of claim 15 wherein the amplified target polynucleotide is contacted with a labeled probe.

17. The method of claim 16 wherein the target polynucleotide is amplified with a polymerase.

18. The method of claim 17 wherein the target polynucleotide is a DNA polynucleotide and the polymerase is a DNA polymerase.

19. A method for detecting a target polynucleotide contained in a sample comprising the steps of:

(a) contacting the sample with a first support which binds to the target polynucleotide;

(b) substantially separating the first support and bound target polynucleotide from the sample;

(c) amplifying the sample with a DNA polymerase;

(d) contacting the amplified target polynucleotide with a second support which binds to the amplified target polynucleotide and also with a labeled probe which binds to the amplified target polynucletide; and

(e) detecting the presence of the amplified target polynucleotide.

20. A kit for detecting a target polynucleotide contained in a sample comprising:

(a) means for substantially separating the target polynucleotide from the sample:

(b) means for amplifying the target polynucleotide;

(c) means for binding the amplified target polynucleotide to a solid support; and

(d) means for labeling the amplified target polynucleotide.

21. The kit of claim 20 wherein:

(a) the means for substantially separating the target polynucleotide from the sample include a first support;

(b) the means for amplifying the target polynucleotide include a polymerase;

(c) the means for binding that amplified target polynucleotide to a solid support include a capture probe which binds to the solid support and to the amplified target polynucleotide; and

(d) a detector probe for labeling the amplified target polynucleotide.

22. The kit of claim 21 further comprising a capture probe which binds to the first support and to the target.

23. The kit of claim 22 wherein the polymerase is a DNA polymerase and the detector probe is labeled.

24. A kit for amplifying a target polynucleotide contained in a sample comprising:

(a) means for substantially separating the target polynucleotide from the sample and

(b) means for amplifying the target polynucleotide.

25. The kit of claim 24 wherein:

(a) the means for substantially separating the target polynucleotide from the sample includes a support which binds to the target polynucleotide and

(b) the means for amplifying the target polynucleotide includes a polymerase.

26. The kit of claim 25 wherein:

(a) the polymerase is a DNA polymerase; and

(b) the means for substantially separating the target polynucleotide from the sample includes a probe which binds to the target polynucleotide and the support.

27. A method for amplifying a target polynucleotide contained in a sample medium comprising the steps of:

(a) contacting the sample medium with reagent comprising a first nucleic acid probe which binds to the target to form a probe-target complex;

(b) contacting the sample medium with a support which binds to the first nucleic acid probe of the probe-target complex;

(c) substantially separating the support and bound probe-target complex from the sample medium;

(d) contacting the support and bound probe-target complex with a second medium;

(e) releasing the probe-target complex into the second medium;

(f) substantially separating the support from the second medium; and

(g) amplifying the target polynucleotide.

28. A method for detecting a target polynucleotide contained in a sample medium comprising the steps of:

(a) contacting the sample medium with reagent comprising a first nucleic acid probe which binds to the target to form a probe-target complex;

(b) contacting the sample medium with a support which binds to the first nucleic acid probe of the probe-target complex;

(c) substantially separating the support and bound probe-target complex from the sample medium;

(d) contacting the support and bound probe-target complex with a second medium;

(e) releasing the probe-target complex into the second medium;

(f) substantially separating the support from the second medium;

(g) amplifying the target polynucleotide; and

(h) detecting the presence of the target polynucleotide.

29. The method of detecting a target polynucleotide of claim 28 wherein the target polynucleotide is amplified with a polymerase.

30. The method for detecting a target polynucleotide of claim 29 wherein the polymerase is a DNA polymerase, an RNA polymerase, a transcriptase, or Qβ replicase.

31. The method for detecting a target polynucleotide of claim 30 wherein the polymerase is a DNA polymerase.

32. The method for amplifying a target polynucleotide of claim 27 wherein the target polynucleotide is amplified with a polymerase.

33. The method for amplifying a target polynucleotide of claim 32 wherein the polymerase is a DNA polymerase.

34. A method for amplifying a target polynucleotide contained in a sample medium comprising the steps of:

(a) contacting the sample medium with a support and a probe which binds to the target polynucleotide and the support;

(b) substantially separating the support and bound probe and target polynucleotide from the sample medium;

(c) contacting the support and bound probe and target polynucleotide with a second medium;

(d) releasing the target polynucleotide into the second medium;

(e) substantially separating the support and bound probe from the second medium: and

(f) amplifying the target polynucleotide.

35. The method for amplifying a target polynucleotide of claim 34 wherein the target polynucleotide is amplified a polymerase.

36. The method for amplifying a target polynucleotide of claim 35 wherein the polymerase is a DNA polymerase, an RNA polymerase, a transcriptase or Qβ replicase.

37. The method for amplifying a target polynucleotide of claim 36 wherein the polymerase is a DNA polymerase.

38. A method for detecting a target polynucleotide contained in a sample medium comprising the steps of:

(a) contacting the sample medium with a support and probe which binds to the target polynucleotide and the support;

(b) substantially separating the support and bound probe and target polynucleotide from the sample medium;

(c) contacting the support and bound probe and target polynucleotide with a second medium;

(d) releasing the target polynucleotide into the second medium;

(e) substantially separating the support and bound probe form the second medium;

(f) amplifying the target polynucleotide; and

(g) detecting the presence of the amplified target polynucleotide.

39. The method for detecting a target polynucleotide of claim 38 wherein the target polynucleotide is amplified with a polymerase.

40. The method for detecting a target polynucleotide of claim 39 wherein the polymerase is a DNA polymerase.

* * * * *

Declassified per 2009 E.O. 13526

Exhibit 9 has been filed under seal under separate cover

IN THE UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

- - - - - - - - - - - - - -X

GEN-PROBE INCORPORATED,

Plaintiff,

VS.

VYSIS, INC.,

Defendant.

- - - - - -- - - - - - - - X

NO.99cv2668 H (AJB)

CONFIDENTIAL

Videotaped Deposition of
JONATHON MICHAEL LAWRIE, Ph.D.
Durham, North Carolina
Thursday, February 15, 2001

Reported by:
Sydney C. Silva, Registered Professional Reporter
File No:

COPY

Ex. 9 Pg. 45

A. No.

Q. Do you know whether there's any reference in the patent to a combination of target capture with a target-specific method of application -- of amplification?

A. This patent here?

Q. Yes.

A. I haven't read it completely, just the pieces you have shown me.

Q. When the patent application was filed, did you have any impression about whether the greatest degree of specificity sensitivity might be obtained by combining target capture with a target-specific method of amplification?

A. I don't remember.

Q. Does that stand to reason at all?

A. I don't think so. I don't know what the thought process would have been back then.

Q. Can you recall any reason that a reference to PCR might have been intentionally omitted from the patent application?

A. Yes.

Q. And what reason was that? Let me, let me start over.

Ex. 9 Pg. 46

Was a reference to PCR intentionally omitted from the patent to the best of your understanding? 14:35:24 14:35:27 14:35:29

A. I don't know. 14:35:30

Q. Were there discussions about whether or not to include a reference to PCR in the patent? 14:35:31 14:35:32

A. I can't remember. 14:35:36

Q. So at Amoco you had a thought about combining target capture with PCR, is that right? 14:35:47 14:35:51

A. Yes. 14:35:54

Q. Gene-Trak then did work in an effort to combine target capture with PCR, is that right? 14:35:55 14:35:58

A. From seeing this here, yes. 14:36:03

Q. Do you have a recollection of that? 14:36:05

A. No. 14:36:07

Q. If there's no reference in the patent to combining target capture with PCR, do you have any explanation as to why it is not there? 14:36:07 14:36:09 14:36:13

A. I believe that it was a separate -- the thought behind this was coming up with new methods of amplification, not old ones. 14:36:15 14:36:17 14:36:19

Q. And you would, for the purposes of what you just said, you classify PCR as an old method of amplification? 14:36:31 14:36:32 14:36:36

A. PCR itself was described in the patent, yes, issued patent. 14:36:37 14:36:40

Q. And your understanding of the 338 patent was that it was directed to other methods of amplification? 14:36:41 14:36:44 14:36:47

A. The, it was, it was directed to the methods disclosed by, you know, the methods separate from PCR. 14:36:48 14:36:54 14:36:59

Q. Those being the methods, for example, as the methods set forth in Example 6 and 7? 14:37:07 14:37:10

A. Yes. 14:37:14

Q. Is it your understanding that the 338 patent then doesn't encompass the combination of target capture and PCR? 14:37:20 14:37:22 14:37:28

MR. BANKS: Object to the form. 14:37:30

A. I couldn't say. 14:37:31

Q. I'm sorry? 14:37:32

A. I couldn't say. 14:37:32

Q. Was it your intention that it encompass the combination of target capture and PCR? 14:37:33 14:37:38

A. I don't know. I can't remember what the intention was in regards to PCR. 14:37:40 14:37:41

Q. However, your recollection of why -- of if there's no -- your explanation of why there 14:37:49 14:37:50

might not be a reference to PCR in the patent is that the patent wasn't intended to cover old methods of amplification such as PCR; is that right? 14:37:53 14:37:56 14:38:03 14:38:06

A. The patent was intended to cover the discoveries by myself, Halbert and King that there should be in some, you know, disclosure back at Amoco. That's what the patent was about. 14:38:07 14:38:09 14:38:15 14:38:16

why PCR was left out I can just speculate. It wasn't what we came with, it was in the previous, it was a previous older method. 14:38:22 14:38:26 14:38:30

Q. You were looking for other things? 14:38:33

A. Yeah. 14:38:36

MR. BOWEN: Let's assume that the patent application for the 330 patent was filed on December 21, 1987. Can we stipulate to that? 14:39:04 14:39:06 14:39:10

MR. BANKS: For which patent? 14:39:16

MR. BOWEN: The 330. 14:39:18

MR. BANKS: The 330? Moving to a different one now? 14:39:20 14:39:21

MR. BOWEN: I'm confused this late in the day, huh? The first application that claimed the combination of target capture and amplification. 14:39:22 14:39:25 14:39:27 14:39:32

Ex. 9 Pg. 49

Example 5 is a linear method? 16:21:41

A. Let's see. 16:21:44

Yes, it is linear. 16:22:29

Q. So Example 5 discloses a linear nonspecific method of amplification? 16:22:31 16:22:34

A. Yes. 16:22:37

Q. So recapping the examples, Examples 1 through 3 disclose capture methods without amplification? 16:22:38 16:22:43 16:22:46

A. Yes. 16:22:48

Q. And Example 4 discloses linear nonspecific amplification? 16:22:49 16:22:53

A. Yes. 16:22:54

Q. Example 5 discloses linear nonspecific amplification? 16:22:55 16:22:59

A. Yes. 16:23:00

Q. Example 6 seeks to describe nonspecific exponential amplification? 16:23:02 16:23:10

A. Let's see. Yes. 16:23:13

Q. And Example 7 describes -- seeks to describe nonspecific exponential amplification? 16:23:18 16:23:22

A. Yes. 16:23:28

Q. Looking back at Column 30, specifically at Lines 30 through 40, which I think is two 16:23:44 16:23:48

Exhibit 10 has been filed under seal under separate cover

CONFIDENTIAL - ATTORNEYS' EYES ONLY

VOLUME: I

PAGES: 1-191

EXHIBITS: 115-132

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

- X

GEN-PROBE INCORPORATED,

Plaintiff,

v. C.A. No.

VYSIS, INC., 99CV2668 H (AJB)

Defendant.

- X

CONFIDENTIAL - ATTORNEYS' EYES ONLY

DEPOSITION of JAMES C. RICHARDS

March 30, 2001

9:51 a.m.

Westin Hotel

70 Third Avenue

Waltham, Massachusetts

Reporter: Michael D. O'Connor, RPR

Ex. 10 P. 51

Plaintiff in the case is Gen-Probe Incorporated and the Defendant in the case is Vysis, Inc.

Do you understand that Vysis is the successor to Gene-Trak Systems?

A. Yes.

Q. Let's discuss your educational background briefly. Vysis has produced some documents in the case which lead me to believe that I know something about your background, but I'd like to confirm it.

Did you obtain a Bachelor of Science in microbiology and chemistry from the University of Illinois?

A. Yes.

Q. When did you graduate?

A. 1970.

Q. Did you obtain a Ph.D. in microbiology and biochemistry from Southern Illinois University?

A. Yes.

Q. When did you obtain that degree?

A. '78, '79.

Q. And after you obtained your Ph.D. from Southern Illinois University, did you do

Q. Do you recall when you left DuPont to go to work for Amoco?

A. Yes.

Q. When was that?

A. December, '84, January, '85; that was the time. I don't know when I left. I think it was before Christmas of '84, but I can't remember exactly.

Q. When you joined DuPont you became program manager for the nucleic acid probe development group?

A. Excuse me, which company?

Q. When you joined Amoco --

A. Amoco, yes.

Q. -- in December of '84, January of '85, you became program manager for the nucleic acid probe development group?

A. I left DuPont December, '84. I started at Amoco February 1 of '85.

Q. Thanks. At that time what job --

A. Program manager, DNA probe development.

Q. Did you stay in that position with Amoco until you left for Gene-Trak?

Ex. 10 Pg. 53

A. Yes.

Q. You left for Gene-Trak sometime in 1986?

A. Roughly October, '86.

Q. So you were at Amoco from February of '85 to October of 1986?

A. Correct.

Q. While you were program manager of the nucleic acid probe development group at Amoco, what kind of work did you or your group do?

A. I was alone and I wrote the business plan for DNA probes for Amoco.

Q. When you say you were alone, there weren't people that reported to you?

A. No. Oh, wait a minute. Time out. I can't remember if Bach and Ryan and the engineers reported to me or Lawrie. It doesn't matter. I was doing business development.

Q. I'd like you to look at Exhibit 38, which aught be the next one in the book behind the '338 patent, which is an organizational chart. This organizational chart has been previously marked in the case as Exhibit 38. It appears to be --

A. Oh, I had sample prep, that's right, and I had the engineers I guess.

MR. BANKS: Let him ask the questions.

A. I'm sorry. I don't remember.

Q. This appears to be an undated organization chart related to the DNA probe effort at Amoco. To the best of your recollection, does this chart, Exhibit 38, reflect the organization of the probe group in 1986?

A. Yes.

Q. Can you tell from looking at this chart who reported to you or does it refresh your recollection?

A. I will tell you, now I remember. Kessler was doing sample prep, and Bach and Ryan in the engineering group were doing the system, and they loosely reported to me. I don't remember Halbert and Dudzik. I thought they reported to Lawrie. The rest of this was all Lawrie. That's why I say, I was working on business development for the most part, and the only reason Bach and Ryan reported to me because I knew them at DuPont, and I hired Jack from

putting enzymes on Mark's target capturing method, removing noise, and generating a higher signal. So we used target capture and signal amplification, i.e., using the ELISA type approach. But we were also doing radioactive labels, and we were, of course, all aware of other things that were out there.

Q. Do you know who at Amoco had the original idea to combine target capture and some form of amplification?

A. It might have been Mark, but I don't remember.

Q. While you were at Amoco, did you ever have the understanding that Collins, King, Halbert and Lawrie had conceived of an invention that involved the combination of target capture and amplification?

A. John mentioned it to me once.

Q. What did he tell you, that you can remember.

A. Well, in writing the business plan, I was always concerned about rare targets, and one day John came into my office -- we were right down the hall at Amoco from each other -- and he

said, we've got a way to make more targets, and he described the method, and I didn't understand the method, because I had never used it in my research, and it was Klenow and some other stuff.

He explained you could do this in a way to make more target, and I said, what about PCR? He said, You could do PCR, but you could also use this, and I said, Well, okay. Sounds good to me, and off he went. That was it. I mean, we didn't pursue it, because we had a clear business structure, and it was target cycling, and an enzyme label, and we were going to go do this new business, and I said, Well, when you get it proven, come and see me basically.

Q. In part of your statement you used the term "rare targets." By that term are you referring to targets that are in a sample in low concentration?

A. Right.

Q. Did you ever have an understanding about how this invention was conceived, whether it was at a brainstorming meeting?

Gene-Trak deal.

Q. Do you remember that the first article on PCR was published in "Nature" in about December, 1985?

A. No, I don't remember that.

Q. When the first article describing PCR was published, was it big news?

A. Yes.

Q. After that article was published, did other people in the industry outside Cetus begin looking for alternative ways to do the same thing?

MR. BANKS: Objection to form.

A. Do I know if they were?

Q. Right.

A. I don't know.

Q. Do you know whether Amoco started to think about what it could do that would be similar to PCR?

A. Amoco owned 25 percent of Cetus at that time, and discussions were running around should we take a license to this, because we owned 25 percent of the company, and that was the extent of the discussion, and that was way

did you live in the Chicago area?

A. '85 to '86, and I lived in Lisle.

Q. Outside of Chicago?

A. Next to Naperville about 100 feet or so; very close, next door.

Q. And when you went to work for Gene-Trak in about October of '86, did you move to the Boston area?

A. Framingham.

Q. Did Halbert, King, Collins and Lawrie also move from Amoco to Gene-Trak?

A. Yes, I believe so.

Q. Prior to the time that Gene-Trak was formed, were you involved in discussions or negotiations concerning the value of the respective contributions that were being made by Amoco and Integrated Genetics?

A. Me involved in the valuation? I don't remember.

Q. Were you involved in the negotiations between Amoco and Integrated Genetics?

A. No. No, as an absolute. Gar Royer and Ed Mason were the main Amoco, I believe, people involved in the face-to-face

A. Yes.
Q. About the same time?
A. About the same time.
Q. And he is shown here as being the manager of scientific affairs?
A. Yes.
Q. In that position, what did he do?
A. He was going to be in charge of clinical trials, setting up the ways -- actually, his primary responsibility was to set up what we called our clinical reference laboratory, where we were going to bring in real clinical samples from patients to do probe capture of pathogens, and it had to be a BL-3 lab, a containment facility. It was literally a full-time job just doing that. We set it up in a separate building.
Q. And as director of business development and licensing at Gene-Trak, what were your responsibilities?
A. Licensing technology, licensing in, licensing out, if we could. If R&D needed something, go out and find it, basically if they needed a new technology, go out and get a

license, constantly assessing the business plan, are we on target, setting milestones, assisting Connoy with the budget, making sure we were achieving our milestones. It's what business development is.

Q. So part of your job was dealing with the technology assets and the technology needs of R&D?

A. Yes, I think that's fair.

Q. Now, the technology assets of a company are sometimes referred to as intellectual property?

A. IP, yes.

Q. IP includes things like patents, trademarks, confidential business information?

A. Mostly in my case it was patents, memoranda of invention, trademarking, I guess, but it was handled mostly by the attorneys.

Q. When you say "patents," that would include issued patents and it would include pending patent applications?

A. In this case, I can tell you it was almost exclusively what we were inventing at Gene-Trak in the form of MOIs, and having them

Q. And you were on that committee?

A. Correct.

Q. And the committee established priorities for filing patent applications based on the memorandum of invention?

A. Not completely. I mean, it had to have a business value. I mean, that's why I was there. Is this going to help us meet our milestones, or is this just extra stuff, but we aren't using it, so therefore, we've got to be working on the things that we need for commercialization. So there's business criteria is how you prioritize these.

Q. So would the patent committee both look at the science of a memorandum of invention and the business application of that science?

A. As it pertained to our existing milestones.

Q. While you were at Gene-Trak, were you involved in any out-licensing activities?

A. I don't remember.

Q. While you were at Gene-Trak, were you involved in any in licensing?

A. Yes.

Q. So in licensing would take place if some other company had technology or intellectual property that Gene-Trak was interested in using in its business?

A. Not just companies, but, yes. It could be universities, whatever. Somebody else owned it.

Q. If somebody else had some technology --

A. That we might need.

Q. -- that Gene-Trak thought might be useful, you would get involved in trying to license that technology for Gene-Trak?

A. Yes.

Q. Did Dr. Klinger get involved in licensing activities?

A. Yes.

Q. Were you involved in the negotiation of most of the licenses that Gene-Trak took?

A. Involved, yes.

Q. Were you involved in evaluating technologies that Gene-Trak was looking at to license?

A. Yes.

Ex. 10 Pg. 63

There were others, other methods.

Q. There were other methods?

A. (Witness nods).

Q. There were other sequence specific methods before PCR?

A. Before PCR? I don't know the timing, but Salk, and there were others.

Q. Looking at Exhibit 45, if a presentation was made to the partnership committee meeting on patents in the summer of '87, is it likely that you made the presentation?

A. Yes.

Q. And if a presentation was made on nucleic acid amplification strategy, is it likely that Dr. Lawrie made the presentation or would you have made it?

A. It probably would have been me. This looks like it would have been me.

Q. Is there anything here that tells you it would have been you or suggests to you it would have been you?

A. Yes, because it looks like it came off of my Macintosh computer, the type. I recognize

of doing nucleic gymnastics. Discrete date, no. I don't have any discrete date or time. It was an ongoing intellectual discussion.

Q. I'd like you to look at, I think it's the fourth page of this pack of schematics, Exhibit 49. It's got a No. 4 in the upper left-hand corner, and it talks about specific capture, apparently followed by nonspecific amplification, and then another specific capture step. Do you see that?

A. Yes.

Q. Did you understand this to be the method that Dr. Lawrie had discussed with you, the Collins method?

A. Do you mean not looking at this?

Q. Right.

A. Yes. Again, the hexadecamer, Klenow, yes, that's what I remember.

Q. Hexadecamer, when you use that term, are you referring to a hexamer primer?

A. It was the one you could buy from commercial sources. They were, I think, random.

Q. So when you're using the term "hexadecamer primer," you're referring to a

commercially available random hexamer primer?

A. That was my understanding of the nonspecific amplification concept.

Q. And that was what you understood Dr. Lawrie to have talked to you about?

A. Among others, yes.

Q. The fourth thought here on the fourth page of Exhibit 49 is a question, "Too close to Cetus." Do you see that?

A. Yes.

Q. Do you have any recollection of there being concern at Gene-Trak that the method of doing specific capture in conjunction with nonspecific amplification might be too close to the PCR method?

A. I don't remember that. This is not my thing. Somebody else did this stuff.

Q. I'd like you to look at what's previously been marked as Exhibit 53, if you would. Exhibit 53, the first page of Exhibit 53 is entitled, "Partnership Committee Meeting, January 23, 1987." Item 7 on the list is "Patent Strategy," and your name appears opposite that.

Ex. 10 Pg. 66

him?

A. Yes.

Q. When presentations on patents were given to the partnership committee, is it your recollection that you gave those presentations?

A. Yes.

Q. Was there a reason that you gave the presentations and not Mr. Janiuk or Mr. Hofer?

A. I don't believe I gave patent presentations. I think I talked about the business implications of what they might reflect. I didn't and don't understand claim language, then or now. I used to mess it up. So I stuck pretty much to the business relationship between the patent and claims and what we were trying to accomplish. I just stuck to the business.

Q. I'd like you to look back at Exhibit 45, please.

A. Yes.

Q. I think you said when we looked at Exhibit 45 before that you're probably the author of Exhibit 45?

A. Yes.

Ex. 10 Pg. 67

A. Yes.

Q. In Step 3A there's a reference to hexamer primers?

A. Yes.

Q. And I think this morning you told me that you would generally consider the reference to hexamer primers to commercially available random hexamer primers?

A. As I understood it, yes.

Q. In looking at that term here and remembering the language that we just looked at in Column 15 about nonspecific amplification, do you understand that reference to hexamer primers to be a reference to random hexamer primers in Figure 5?

A. Well, if they are random hexamer primers, yes, I guess that would be what I was led to believe.

Q. Random hexamer primers would be used in nonspecific amplification?

A. Right. That's what John had led me to believe back when.

Q. Turning to Figure 6, again, in Step 3A, there's a reference to hexamer primers. Do

specially tailored primers are needed, do you have any understanding why someone would then use specific primers?

MR. BANKS: Object to form.

A. You would want to use any kind you could, not just specific, nonspecific; anything. You would want all aspects.

Q. Looking at example four, the last paragraph, which is in Column 31, about Line 16 --

A. I'm sorry, repeat where the location is?

Q. About Line 16 of Column 31.

A. Okay.

Q. There's a reference there to the resulting nonspecific transcription. Do you see that?

A. Yes.

Q. Example five, the first paragraph, do you see that it refers to nonspecific replication?

A. Oh, I see it.

Q. Is it your understanding that example five is describing a method in which nonspecific

primers are used?

MR. BANKS: Object to form.

A. That's what it says, I think.

Q. The same with example six. Do you see in example six, which is Column 31, at about Line 63, the example refers to the use of random hexamer primer oligonucleotides?

A. Right.

Q. Example six is a method describing nonspecific primers?

MR. BANKS: Object to form.

Q. Is that correct?

A. I'm reading it, yes.

Q. And example seven, which is Column 32, at about Line 13, it talks about replicating nonspecifically. Do you see that?

A. What it says is it's a precise transcript is purified. I'm reading it, but I'm not sure in this case what the specificity is imparted. The hybrid duplex is then denatured. I can read. I'm not sure what the -- I have to look at the -- is there a figure for this?

Q. I don't think that there is.

A. It sounds like there's specificity

involved in the capture probe. I'm sorry, what's the question in No. 7?

Q. Is it your understanding that the amplification step in example seven uses nonspecific primers?

A. Does it use nonspecific primers? It appears that's what it says.

Q. So when we look at examples five, six and seven, all of them use nonspecific primers in the amplification step?

A. In some aspect.

MR. BOWEN: Take a five-minute break.

VIDEOGRAPHER: Off the record. The time is 2:04.

(Recess)

VIDEOGRAPHER: Back on the record. The time is 2:17.

BY MR. BOWEN:

Q. Dr. Richards, when you were at Gene-Trak, did you ever have an understanding that Gene-Trak, as an organization, thought that using random primers and target capture might be a method that was more suitable for automation than PCR?

Ex. 10 Pg. 71

patents to the partnership committee, the management committee of Gene-Trak, you were the person who made the presentations?

MR. BANKS: Object to form.

MR. BOWEN: What don't you like about it?

MR. BANKS: Lack of foundation.

MR. BOWEN: Okay.

Q. When presentations on patents were made to the partnership committee, did you make the presentations?

A. Yes.

Q. And you did that about once a quarter?

A. Yes.

Q. You had been on the patent committee? By December of 1989, you had been on the patent committee for Gene-Trak for a number of years?

A. Yes.

Q. You had access to and discussed patent matters with Gene-Trak's patent counsel?

A. Yes.

Q. You discussed the application for the '338 patent with Gene-Trak's patent counsel?

A. I don't remember.

Ex. 10 Pg. 72

Q. You made presentations on target capture patents to the scientific advisory board of Gene-Trak?

A. Yes.

Q. Let me show you what we will mark as Exhibit 121, which is a document entitled at the top "Business Development, August 3, 1988."

Do you believe you prepared Exhibit 121?

(Document marked as Exhibit 121 for identification)

A. I believe so, yes.

Q. Exhibit 121 is an evaluation of patents and licenses?

A. Yes.

Q. You evaluated these technologies as part of your job as director of business development and licensing?

A. Yes.

Q. In December, 1989, what were your sources of understanding about what the pending patent application for the technology that's covered by the '338 patent was about? What were your sources of information for your

understanding?

A. What date?

Q. December, 1989.

A. What was my understanding?

Q. As of December, 1989, did you have an understanding about what technology was covered by the '338 patent?

A. Yes.

Q. What were your sources of information for that understanding?

A. My recollection of my conversations with John years before, and just simply a nonspecific way of amplifying.

Q. I will show you what we will mark as Exhibit 131 to your deposition. Last week, did you remember writing a letter to Dr. Orgell in December, 1989 concerning the subject matter of the '338 patent?

(Document marked as Exhibit 131 for identification)

A. Last week?

Q. Yes.

A. I do not remember seeing this until I saw it the other day.

Ex. 10 Pg. 74

Dr. Orgell --

A. Orgell.

Q. -- Amoco was a partner in Gene-Trak?

A. Yes.

Q. Amoco owned half of Gene-Trak; is that right?

A. A large percentage. I don't remember how much.

Q. And Dr. Orgell was the general manager of research at Amoco Technology?

A. Yes.

Q. In the corporate ladder, is Dr. Orgell up the ladder from you?

A. Oh, yes. He's Amoco. I was not in Amoco.

Q. He worked directly at Amoco?

A. No. I was a Gene-Trak employee.

Q. Amoco owned half of Gene-Trak?

A. Yes.

Q. Did you consider Dr. Orgell, in any sense, to be one of your bosses?

A. I considered him like a venture capital -- I mean, he's a finance -- he's one of the people that bankrolls the company, and a guy

I have to convince to pursue technology.

Q. Looking at the people who received ccs of this letter, Patrick Connoy was your boss at Gene-Trak?

A. Yes.

Q. Dr. Royer was another bigwig at Amoco Technology?

A. He was my boss at Amoco.

Q. He was on the Gene-Trak scientific advisory board?

A. Yes.

Q. He had been at scientific advisory board meetings where you made presentations on the target capture patents?

A. Yes.

Q. Was he also on the partnership committee?

A. Yes.

Q. Was Dr. Orgell on the partnership committee?

A. No, not that I remember.

Q. Now, a cc apparently of this letter, Exhibit 131, also apparently went to Mr. Carpenter?

Ex. 10 Pg. 76

A. Yes.

Q. I think you've already said that he was the president of Gene-Trak and worked at Integrated Genetics and then Gensyme?

A. Yes.

Q. At some point in time Integrated Genetics merged with Gensyme; is that right?

A. Yes.

Q. When you wrote letters to Dr. Orgell and sent copies to Mr. Connoy and Dr. Royer and Mr. Carpenter, did you try to be accurate?

A. I tried to be accurate, yes.

Q. I'd like you to look at Page 1 of the letter. You had a chance, when you went with Mr. Banks, to read your description here on Pages 1 and 2 of Technology Asset No. 1?

A. Yes.

Q. And after reading that, did you have the understanding that what's set forth here is a discussion of the subject matter of the '338 patent?

MR. BANKS: Object to form.

A. I only knew this then as however I reference -- I don't know. It's just something

of that ever change your understanding about what the patent covered?

A. I'm sorry.

Q. That was a terrible question, wasn't it.

A. I don't understand.

Q. Whether you were right or wrong, the letter sets forth your impression at the time of what technology was covered by a patent application that was pending?

MR. BANKS: Object to form.

A. I will repeat this again. I assumed this was the same stuff John had talked to me about years before. I didn't want to see it drop. It's that simple. There isn't any more or less to it.

Q. The letter does, though, set forth your understanding of what the technology was?

A. Yes, as I understood it, and as I could relay it.

Q. Did your understanding ever change after you wrote the letter?

A. No, I don't think so.

Q. Did anybody who got a copy of the

letter call you or write you and tell you you had inaccurately described the technology?

A. I don't remember. I don't remember. I don't even know if they read it.

Q. But you don't remember anybody calling you --

A. I don't remember that.

Q. I'm sorry, I've got to get the whole question out.

You don't remember anybody calling you and telling you you had incorrectly described the technology?

A. I don't remember.

Q. As you sit here today, do you have any reason to believe that you misunderstood the technology covered by the pending patent application?

A. No. I think it's -- what I've read, no.

Q. Do you know why there's no reference in the patent to PCR type amplification?

A. No. I didn't write it.

Q. Now, in 1986/1987, a scientist who was going to use nonspecific amplification would

come from Tony. But this stuff on and on, you go on. Temperature required, another approach would be to transcriptase. All of this was free form text writing. I was trying to sell Carl Orgell to pick this thing up. I didn't want to get too technical, or he would put it down, which is probably what everybody did anyway.

Q. You wanted to be accurate in describing --

A. Tried to be as accurate as possible.

Q. We've talked about Tony here in our recent conversations. Tony was Tony Janiuk?

A. Yes.

Q. And he was Gene-Trak's patent counsel?

A. He sat across the way.

Q. Yes, he was Gene-Trak's patent counsel?

A. Yes.

Q. And you had discussions with him about the CIP application?

A. Yes, clearly.

Q. In 1989, did you have any understanding at all of the term "reduction to practice"?

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC., Defendant.	No. 99cv2668 H (AJB) **PROOF OF SERVICE**

PROOF OF SERVICE
(FRCP 5)

I am a citizen of the United States and a resident of the State of California. I am employed in San Diego, State of California, in the office of a member of the bar of this Court, at whose direction the service was made. I am over the age of eighteen years, and not a party to the within action. My business address is 4365 Executive Drive, Suite 1100, San Diego, California 92121-2128. On the date set forth below I served the documents described below in the manner described below:

1. NOTICE OF MOTION AND MOTION OF GEN-PROBE INCORPORATED FOR PARTIAL SUMMARY JUDGMENT;
2. MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT;
3. SEPARATE STATEMENT OF UNDISPUTED FACTS IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT;
4. DECLARATION OF R. WILLIAM BOWEN IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT
5. DECLARATION OF DR. JOSEPH D. FALKINHAM IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT
6. DECLARATION OF DR. MATTHEW LONGIARU IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT
7. STIPULATION AND [PROPOSED] ORDER ALLOWING GEN-PROBE INCORPORATED TO FILE UNDER SEAL CERTAIN DOCUMENTS UPON WHICH IT RELIES TO SUPPORT ITS MOTION FOR PARTIAL SUMMARY JUDGMENT
8. NOTICE OF LODGMENT IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT

☐ (BY U.S. MAIL) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of correspondence for mailing with the United States Postal Service, and I caused such envelope(s) with postage thereon fully prepaid to be placed in the United States Postal Service at Palo Alto, California.

☐ (BY MESSENGER SERVICE) by consigning the document(s) to an authorized courier and/or process server for hand delivery on this date. See attached Proof of Personal Service.

☐ (BY FACSIMILE) I am personally and readily familiar with the business practice

of Cooley Godward llp for collection and processing of document(s) to be transmitted by facsimile and I caused such document(s) on this date to be transmitted by facsimile to the offices of addressee(s) at the numbers listed below.

☑ (BY OVERNIGHT MAIL) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of correspondence for overnight delivery, and I caused such document(s) described herein to be deposited for delivery to a facility regularly maintained by Federal Express for overnight delivery.

on the following part(ies) in this action:

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VIA FACSIMILE AND MAIL

Executed on April 30, 2001, at San Diego, California.

Liz Hoke

PROOF OF PERSONAL SERVICE

I hereby declare:

I am employed in the City of San Diego, County of San Diego, California; I am over the age of eighteen years and not a party to the within cause; my business address is Knox Attorney Service, 2250 Fourth Avenue, San Diego, California 92103.

On April 30, 2001, I served the within document(s):

1. **NOTICE OF MOTION AND MOTION OF GEN-PROBE INCORPORATED FOR PARTIAL SUMMARY JUDGMENT;**
2. **MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT;**
3. **SEPARATE STATEMENT OF UNDISPUTED FACTS IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT;**
4. **DECLARATION OF R. WILLIAM BOWEN IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT**
5. **DECLARATION OF DR. JOSEPH D. FALKINHAM IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT**
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8. **NOTICE OF LODGMENT IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT**

on the interested parties in this action by personally hand delivering a copy of said document(s) to the address(es) listed below:

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I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct, and that this declaration was executed on April 30, 2001.

SIGNATURE: _____

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

VYSIS' OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

TABLE OF CONTENTS

TABLE OF AUTHORITIES

FEDERAL CASES

I. INTRODUCTION

The circumstances leading to commencement of this suit by Gen-Probe Incorporated ("Gen-Probe") require close scrutiny of its myriad allegations that the patent in suit, owned by Vysis Inc. ("Vysis"), is invalid and not infringed. Having failed to appreciate the value of the present invention until **after** Vysis suggested its value to Gen-Probe in 1994, having thereafter adopted the patented technology as solving the problems that Gen-Probe itself concedes had been the "Achilles' heel" of earlier assay products, having insisted that it be granted a license under the Vysis patent as a condition to settlement of prior unrelated litigation between the parties, and having to this day scrupulously preserved for itself the protections provided by the license, Gen-Probe now comes before this Court seeking to avoid its obligations to pay royalties under that license agreement. Gen-Probe does so by presenting a series of factual and legal contentions that are irreconcilable with its own conduct, the clear prosecution history of the patent in suit, and well settled patent law.

The allegations upon which Gen-Probe's present motion for summary judgment is based cannot withstand close scrutiny. Gen-Probe asks this Court to read into the Vysis patent claims a requirement for non-specific amplification. Yet, when the available intrinsic evidence that must be considered in all matters of claim construction – the claims, the patent specification, and the prosecution history – point unambiguously in the other direction. The text of the patent makes specific reference to "specially tailored primers" of the sort used in specific amplification processes, the patent owner stated repeatedly during prosecution leading to issuance of the patent that "[t]argets can be amplified by a number of ways including PCR," which is perhaps the most notorious specific amplification technique of all, and the U.S. Patent and Trademark Office (PTO) specifically stated in its reasons for allowance of the patent that it related to "PCR amplification." A fatal flaw in Gen-Probe's motion is the complete failure even to address the prosecution history of the patent. Much of the material offered by Gen-Probe in support of its position falls instead into the category of "extrinsic" evidence, including alleged evidence of the inventors' subjective intent, which the Federal Circuit has repeatedly indicated should not be considered on the issue of claim construction. Under these circumstances, Gen-Probe's suggestion that the patent claims should be read in a way

that would exclude specific amplification techniques, such as PCR, borders on the frivolous and must be rejected as a matter of law.

II. THE CLAIMS OF THE '338 PATENT ARE NOT LIMITED TO NON-SPECIFIC AMPLIFICATION

A. Claim Construction Requires Review of the Prosecution History of the Patent

In its effort to ignore the prosecution history of the patent in suit -- U.S. Patent No. 5,750,338 ("the '338 patent") -- Gen-Probe badly misstates the law applicable to claim construction. Citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996), Gen-Probe makes the following statement in its memorandum:

> In determining the proper construction of a claim, the Court has numerous sources that it may properly utilize for guidance. Cite omitted. These sources include both "intrinsic" evidence (e.g., the patent specification) and "extrinsic" evidence (e.g., expert testimony and the inventor's/patent owner's own descriptions of the invention).

Gen-Probe Memorandum ("Memo.") at 8.

Gen-Probe's statement of the applicable law is a gross mischaracterization of what the *Vitronics* court actually said. The court said:

> In determining the proper construction of a claim, the court has numerous sources that it may properly utilize for guidance. These sources . . . include both intrinsic evidence (e.g., the patent specification **and file history**) and extrinsic evidence (e.g., expert testimony).

Id. (emphasis added). The *Vitronics* court went on to state that the prosecution (or file) history "is often of **critical significance** in determining the meaning of the claims." *Id.* (emphasis added). Indeed, the *Vitronics* court concluded that "it is **improper** to rely on extrinsic evidence" when "the intrinsic evidence alone will resolve any ambiguity in a disputed claim term." *Id.* at 1583 (emphasis added). [1]

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[1] In a further attempt to obscure the importance of the prosecution history to claim construction, Gen-Probe, at page 13 of its Memo, also crops a quote from *Wright Medical Technology, Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1443 (Fed. Cir. 1997). Gen-Probe quotes from the case: "The proper construction of the claims is based upon the claim language, the written description portion of the specification including any relevant drawings . . ." but omits the court's reference to the "prosecution history."

The Federal Circuit's seminal claim construction case of *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996), held that a patent's prosecution history "is of **primary significance** in understanding the claims." (Emphasis added.) Indeed, the Federal Circuit has stated that the failure to consider the prosecution history during claim construction is error. *Lemelson v. United States*, 752 F.2d 1538, 1550 (Fed. Cir. 1985).

This Court, citing *Markman*, has recognized that courts **must** consider the prosecution history, if in evidence, when construing patent claims, along with the claims themselves and the specification. *Lee's Aquarium & Pet Products, Inc. v. Python Pet Products, Inc.*, 951 F. Supp. 1469, 1472 (S.D. Cal. 1997), *aff'd*, 152 F.3d 945 (Fed. Cir. 1998). In that case, this Court also agreed with *Vitronics* that it is improper for the court to rely on extrinsic evidence if an analysis of the intrinsic evidence (claim language, specification, and prosecution history) resolves any ambiguity. *Id.*

The Federal Circuit in *Markman* eloquently explained why the type of evidence offered by Gen-Probe has little or no weight in determining the scope of a claim and why the prosecution history of a patent is intrinsic evidence that must be considered in claim construction:

> No inquiry as to the subjective intent of the applicant or PTO is appropriate or even possible in the context of a patent infringement suit. The **subjective intent of the inventor** when he used a particular term **is of little or no probative weight** in determining the scope of a claim (**except as documented in the prosecution history**). . . . While presumably the inventor has approved any changes to the claim scope that have occurred via amendment during the prosecution process, **it is not unusual for there to be a significant difference between what an inventor thinks his patented invention is and what the ultimate scope of the claims is after allowance by the PTO**. [Citation omitted.] Of course the views of the other party to the "patent contract," the government, are generally not obtainable, **except as reflected in the prosecution history**. . . .
>
> Moreover, ideally there should be no "ambiguity" in claim language to one of ordinary skill in the art that would require resort to evidence outside the specification and prosecution history. . . . Patent applications, unlike contracts, are reviewed by patent examiners, quasi-judicial officials trained in the law and presumed to "have some expertise in interpreting the [prior art] references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents." [Citations omitted.] **If the patent's claims are sufficiently unambiguous for the PTO, there should exist no factual ambiguity when those same claims are later construed by a court of law in an infringement action**.

Markman, 52 F.3d at 985-86 (emphasis added).

Gen-Probe completely ignores the clear pronouncements in these binding precedents that the prosecution history is intrinsic evidence that must be considered in determining the meaning of a patent claim and instead relies heavily on the inventor's/patent owner's recollections of the invention that the courts have held are extrinsic evidence not normally considered in claim construction. Why Gen-Probe did this is clear. An examination of the prosecution history of the '338 patent unambiguously establishes that the PTO and the patent owner both believed that specific amplification was included in the invention claimed by the '338 patent, which is fatal to Gen-Probe's motion.

B. The Prosecution History Belies Gen-Probe's Asserted Claim Construction

The claims of the '338 patent are directed to methods or kits for amplifying or detecting a target polynucleotide in a sample by combining the techniques of target capture with amplification. As Gen-Probe correctly points out in its memorandum, the claims include the step of "amplifying" the target polynucleotide. Gen-Probe argues that the proper meaning of the term "amplifying" in the claims is limited to non-specific amplification. The prosecution history of the '338 patent, however, unambiguously belies Gen-Probe's contention.

The prosecution history of the '338 patent, the history of the correspondence between the patent owner and the PTO, leads to the inescapable conclusion that both the patent owner and the PTO (no fewer than five different Patent Office Examiners) considered the claimed invention to encompass the polymerase chain reaction ("PCR"), which is a type of specific amplification.[2]

The initial application for the '338 patent included a broad claim (claim 1), which recited the step of "subjecting said removal product to amplification . . . ." Exhibit ("Ex.") A to Declaration of Thomas W. Banks in Support of Vysis' Opposition to Gen-Probe's Motion for Partial Summary Judgment ("Banks Decl."), p. 61.[3] In rejecting the claims of the original '338 patent application in

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[2] The following discussion of the prosecution history is based primarily on the Declaration of David H. Persing In Support Of Vysis' Opposition To Gen-Probe's Motion For Partial Summary Judgment ("Persing Decl.").

[3] It is noteworthy in this regard that original dependent claim 11 contained language specifically further limiting the claim to "non-specific" amplification, which language was never incorporated into the broad claims. Banks Decl., Ex. A. The patent owner clearly knew how to exclude the disclosed use of specific amplification had it wanted to, but did not.

the PTO's first Official Action, Patent Examiner Scott A. Chambers, Ph.D, and Primary Patent Examiner Amelia Burgess Yarbrough cited as prior art the basic Mullis PCR patents. Banks Decl., Ex. B, pp. 3-4. Clearly, if the Patent Examiners had believed that the claims of the '338 patent application were limited to non-specific amplification, it would have been illogical for them to have cited the PCR patents against the application, because PCR is a type of specific amplification. Thereafter, Examiner Chambers and Primary Examiner Margaret Moskowitz continued to cite the Mullis PCR patents against the pending patent claims. Banks Decl., Ex. C, p.3, and Ex. D, p.3.

In responding to rejections of the pending claims based on the Mullis PCR patents, the owner of the '338 patent never attempted to distinguish the Mullis patents by arguing that Mullis disclosed specific amplification, whereas the invention of the '338 patent was directed to non-specific amplification. To the contrary, the patent owner repeatedly emphasized that the invention included PCR-type amplification:

> Applicant's invention principally serves to enhance the sensitivity of nucleic acid hybridization assays utilizing target amplification. **Targets can be amplified by a number of ways including PCR**. Applicant's invention enhances sensitivity by eliminating from the amplification medium extraneous (nonspecific) nucleic acids which might otherwise be amplified by PCR thereby introducing noise into the assay.

Banks Decl., Ex. E, p.18 (responding to November 5, 1992 Office Action in application serial no. 07/944,505) (emphasis added).

If the patent owner had considered the invention to be limited to non-specific types of amplification, it undoubtedly would have argued this to the PTO to overcome the rejection of the patent claims based on the Mullis PCR patents, which disclosed specific amplification. Instead, the patent owner maintained all along that the invention encompassed PCR and argued that the invention was not obvious in view of the PCR patents. Persing Decl., ¶ 16.

The official recognition that the '338 patent claims encompassed specific amplification techniques like PCR persisted through the very end of the patent procurement process. Indeed, Patent Examiner Dianne Rees, Ph.D., and Primary Patent Examiner W. Gary Jones make it clear in the very first sentence of their Examiner's Statement of Reasons for Allowance that they considered the claims of the '338 patent to encompass specific amplification techniques such as PCR:

> The claims are drawn to methods of **PCR amplification** wherein the target is first separated from the sample by using a support that binds to the target polynucleotide and then amplified.

Banks Decl., Ex. F, p.2 (emphasis added).

The only reasonable conclusion to be reached upon reading the prosecution history of the '338 patent is that both the patent owner and the five patent examiners who examined the patent application believed that the term "amplify" in the patent claims included specific amplification. Persing Decl., ¶ 18.

If the PTO's views from the original prosecution history were not enough, the PTO has adhered to these views in reissue proceedings. In its Protest to Vysis' reissue application for the '338 patent, Gen-Probe presented to the PTO the argument set forth in this motion that the specification of the '338 patent does not provide a basis for claiming specific amplification after target capture. The PTO has indicated that it disagrees with Gen-Probe's interpretation of the '338 patent, stating in a January 16, 2001 Interview Summary that "the specification [of the '338 patent] provided basis for both specific and non-specific amplification of targets subsequent to capture." Banks Decl., Ex. G, pp. 3-4.

The Federal Circuit has made it clear that the Patent Examiner's understanding of the meaning of patent claims developed during prosecution is relevant to construing the proper scope and meaning of those terms. *Markman*, 52 F.3d. at 983 ("It is evident from Markman's explanation of the claims to the examiner that he used 'inventory' in the patent and the examiner understood 'inventory' to consist of 'articles of clothing.'"); *Toro Co. v. White Consolidated Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999) ("Determining the limits of a patent claim requires understanding its terms in the context in which they were used by the inventor, considered by the examiner, and understood in the field of the invention.").

Federal District Courts, including this Court, have followed the Federal Circuit's direction and relied on the meaning of claim terms adopted by the PTO during patent prosecution in construing the meaning of patent claims. *Synthes v. Depuy Ace Medical Co.*, 1999 U.S. Dist. LEXIS 18173, *12-16 (E.D. Pa. 1999) (court declined to construe patent claim terms narrowly because Patent Examiner had rejected the claims based on prior art that met those terms only if construed

broadly); *Sport Squeeze, Inc. v. Pro-Innovative Concepts, Inc.*, 51 U.S.P.Q.2d 1764, 1769 (S.D. Cal. 1999) ("the prosecution history of all three patents reveals that both [the inventor] and the patent examiner understood that differing particle sizes were significant in light of [the prior art]").

Here, the case is even stronger than in *Synthes* for refusing the proferred narrow construction of the disputed claim language. The Patent Examiners of the '338 patent application rejected the claims in view of prior art disclosing the very embodiment, specific amplification, that Gen-Probe contends should not be included within the term "amplify." The patent owner, in response, explicitly acknowledged that the claims encompassed specific amplification techniques, such as PCR. Moreover, in the **very Reasons for Allowance** of the claims of the '338 patent, the PTO Examiners clearly stated their position that the claims included specific amplification, such as PCR.

The prosecution history of the '338 patent makes it clear that not only the patent owner but also the PTO considered specific amplification as included within the claimed term "amplify." As the Federal Circuit observed in *Markman*, "[i]f the patent's claims are sufficiently unambiguous for the PTO, there should exist no factual ambiguity when those same claims are later construed by a court of law in an infringement action." *Markman*, 52 F.3d at 986.

C. The Specification of the '338 Patent Does Not Limit the Claims to Methods Using Non-Specific Amplification

The reason for this unambiguous construction of the patent claims during prosecution as encompassing specific amplification becomes clear from a review of the patent specification. As pointed out in detail below, the specification of the '338 patent describes as one of the particular benefits of the invention that it **permits** the use of non-specific amplification. Gen-Probe, however, points to nothing in the '338 specification that in any way states that non-specific amplification **is** the invention or **must** be used.

1. The '338 Patent Specification

The primary discussion of the invention of combining target capture with amplification begins at column 30, line 15 of the '338 patent specification.[4] The invention is first defined broadly by the statement that "[t]he sensitivity of the above DNA or RNA target capture methods can be enhanced by **amplifying** the captured nucleic acids." (Emphasis added.) The specification then describes a particular benefit of the invention, that "[t]his **can be** achieved by non-specific replication using standard enzymes . . . ." (Emphasis added.) The specification does **not** say that enhanced sensitivity of the target capture methods **is** achieved by non-specific amplification, but rather uses **permissive** language, i.e., that enhanced sensitivity **can be** achieved by non-specific amplification.

The specification then again describes the invention as including amplification generally in the paragraph at column 30, lines 23-29. The paragraph following this describes both specific and non-specific amplification, but points out the particular benefits of the invention when using non-specific amplification:

> Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, **can** employ non-specific enzymes or printers (i.e. enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence). Although any background, non-target, nucleic acids are replicated along with target, this is not a problem because most of the background nucleic acids have been removed in the course of the capture process. Thus **no specially tailored primers are *needed*** for each test, and the same standard amplification reagents can be used, regardless of the targets.

Col. 30, lines 30-40 (emphasis added).

The reference to "specially tailored primers" is an explicit reference to specific amplification techniques. The specification does not say that such specific techniques cannot be used. Rather, the '338 specification simply shows that the use of target capture in accordance with the invention **makes it possible** to use non-specific primers (i.e., non-specific amplification). Without target capture prior to amplification, non-specific amplification would not be a viable technique for

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[4] The following description of the specification of the '338 patent is based on the Persing Declaration.

detecting target nucleic acids in a sample because non-specific amplification causes the replication of virtually any nucleic acid sequence. However, this is not a problem because the invention of the '338 patent provides a target capture step that removes background, non-target nucleic acids from the sample prior to amplification. The specification does not state that one would not want to use specially tailored primers, but only that such primers are **not needed** in this invention. Thus, the specification simply discloses an important advantage of the invention, that is, because of the preceding target capture step, either specific or non-specific amplification can be successfully used in nucleic acid detection assays; whereas without the invention, only specific amplification could be used. Persing Decl., ¶ 11.

The disclosure at column 30, lines 15-40 of the '338 patent specification tells those of ordinary skill in the art that, while the use of target capture made it possible to use non-specific amplification in assays for detecting nucleic acids, the invention was more generally directed to the use of target capture prior to either specific or non-specific amplification. The benefits of the invention, i.e., purifying the sample by removing non-target materials such as contaminants and inhibitors that can interfere with the amplification step, would also be obtained with specific amplification. If the inventors had wanted to limit the invention to non-specific amplification, it is difficult to imagine that they would have drafted the specification as they did. Persing Decl., ¶ 12.

Gen-Probe acknowledges, as it must, the **permissive** rather than **mandatory** disclosure of the '338 patent specification regarding non-specific amplification:

> The inventors . . . pointed out that one of the express benefits of their invention was that it **permitted** the use of non-specific enzymes and non-specific primers.

Memo, p. 11.

Gen-Probe argues that the examples of the '338 patent disclose only non-specific amplification and relies on the declaration of Dr. Joseph Falkinham, wherein he stated that "the primers described in the ['338] patent are not pre-selected to bind to specific nucleotide sequences as part of the amplification process" and that Example 5 describes only non-specific amplification. Memo, pp. 11-12, and Falkinham Declaration ("Decl."), ¶ ¶ 14 and 31.

Contrary to Gen-Probe's contentions, however, Example 5 of the '338 patent **does** disclose the use of a specific primer. In particular, while Example 5 states initially that random oligohexamer primers can be used to achieve non-specific amplification, Example 5 also discloses that "[a]lternatively, the double stranded DNA can be formed by synthesis starting from capture probe a." Col. 31, lines 48-49. In this instance, the capture probe acts as the primer. Since the capture probe binds specifically to the target DNA, the capture probe would be a specific primer to the target. This is an example of specific amplification because the primer, capture probe a, binds to a specific, unique DNA sequence in the target organism. Persing Decl., ¶ 13.

The **most** that can be said of the specification of the '338 patent in support of Gen-Probe's position is that it describes specific amplification as not being the preferred embodiment of the invention. It is well settled, however, that patent claims should not be read as excluding disclosed but not preferred embodiments of the invention. *Tate Access Floors, Inc. v. Maxcess Technologies, Inc.*, 222 F.3d 958, 966 (Fed. Cir. 2000)

2. Gen-Probe's Cited Authority Relates to Descriptions of The Invention Using Mandatory Rather Than Permissive Language

The cases relied on by Gen-Probe in support of its argument are easily distinguishable in that each involved a patent specification that described a particular embodiment not as a preferred embodiment, but as the invention itself. In *Wang Laboratories, Inc. v. America Online, Inc.*, 197 F.3d 1377 (Fed. Cir. 1999), the patent specification always described the disputed term "frame" as being specific to "characters." Thus, the court concluded that the term included "character-based systems" but not "bit-mapped display systems." *Wang* at 1381. In contrast to *Wang*, the '338 patent specification clearly describes the embodiment of non-specific amplification in permissive and not mandatory language. Moreover, in *Wang*, unlike here, the only mention in the specification of the alternative embodiment ("bit-mapped display systems") was in the Background of the Invention, which the court viewed as simply an acknowledgement of the state of the art and not an enlargement of the invention. *Wang* at 1382. In contrast, here specific amplification is described in the patent examples.

Finally, the prosecution history in *Wang* supported the limitation to character-based frames. During prosecution the patent applicant had distinguished prior art on the basis that it "encodes pictorial information . . . on the pel [picture element] level, rather than on the character level." *Wang* at 1384. Here, in contrast, the prosecution history makes it clear that the Patent Office (five different Patent Examiners) and the patent owner all considered the embodiment that Gen-Probe argues should be excluded from the claim, specific amplification, to be within the scope of the claimed invention.

In *Scimed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337 (Fed. Cir. 2001), also relied on by Gen-Probe, the patent specification unequivocally described the embodiment of a **coaxial** lumen structure as the "basic sleeve structure for all embodiments of the present invention contemplated and disclosed herein." *Scimed* at 1339. The court added that "from the outset the specification identifies the inflation lumen, as that term is used in the Scimed patents, as annular, i.e., **coaxial** rather than **dual** in structure." *Scimed* at 1342 (emphasis added). Accordingly, the court limited the scope of the asserted claims to catheters with **coaxial** lumens and held that the patent disclaimed **dual** lumens. *Scimed* at 1340. In contrast to the '338 specification, the specification in *Scimed* used mandatory rather than permissive language making it clear that the invention **was** the use of coaxial lumens, not dual lumens. Also, unlike the present case, the specification in *Scimed* distinguished the invention from prior art that disclosed dual lumens and pointed out the advantages of coaxial lumens. *Scimed* at 1342-43. Finally, unlike here, the court noted that there was nothing pertinent to the issue of claim construction in the prosecution history. *Scimed* at 1340.

In *O.I. Corp. v. Tekmar Co.*, 115 F.3d 1576 (Fed. Cir. 1997), also relied on by Gen-Probe, the issue was the proper meaning of the claim term "passage." All of the "passage" structures contemplated by the specification were either non-smooth or conical. In addition, the specification distinguished the invention from prior art geometries by stating:

> A number of **different geometries** for the second section **are contemplated**, including those having an **irregular shaped** surface or **noncylindrical** shape. **In contrast**, the **prior art** has generally specified that the pneumatic tubing and passageways between the trap and GC are **smooth-walled**.

O.I. Corp. at 1581 (emphasis added). Thus, *O.I. Corp.* is easily distinguishable from this case. Here, the specification of the '338 patent did not distinguish the invention from prior art disclosing specific amplification.[5] The *O.I. Corp.* court also noted that there was nothing identified in the prosecution history contrary to these limiting statements. Based on the specification, the court held that the term "passage" did not encompass a smooth-walled, completely cylindrical structure. *O.I. Corp.* at 1581.

Kraft Foods, Inc. v. International Trading Co., 203 F.3d 1362 (Fed. Cir. 2000), also relied on by Gen-Probe, is also readily distinguishable from this case. In that case, the court relied on the unequivocal statement in the patent specification that "any of the back panels would be constructed of a relatively stiff material" in holding that the claimed "back panel" needed to be "relatively stiff." *Kraft* at 1367. The language in the specification in *Kraft* was mandatory, rather than permissive as in this case. Moreover, in *Kraft*, the prosecution history supported the narrow claim construction because the examiner acknowledged during prosecution that the specification provided a description of the back panel material as being stiff. *Kraft* at 1369.

Because the specification of the '338 patent describes non-specific amplification with permissive rather than mandatory language and also describes the use of specific amplification, the '338 patent specification differs significantly from the specifications in the cases relied on by Gen-Probe, which described a particular embodiment as **being** the invention. The specification of the '338 patent simply points out the benefits of the invention in **permitting** the use of non-specific amplification. It does not limit the invention to non-specific amplification and does not exclude specific amplification. Those skilled in the art reading the '338 patent specification would understand that the invention includes specific amplification. Persing Decl., ¶¶ 7, 19.

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[5] In fact, when faced with rejections based on prior art disclosing PCR, a type of specific amplification, the owner of the '338 patent declined to limit the invention to exclude specific amplification and instead acknowledged that the invention included PCR.

D. Gen-Probe's Extrinsic Evidence Should Be Given No Weight

1. The Falkinham Declaration Should Be Given No Weight Because He Did Not Consider The Prosecution History

Gen-Probe relies on a declaration by Joseph Falkinham stating his opinion that one of ordinary skill in the art would have understood the term "amplifying" as used in the claims of the '338 patent to mean amplifying by use of non-specific amplification, and would not have understood the term "amplifying" to mean amplifying by use of sequence-specific amplification methods. Falkinham Decl., ¶¶ 5, 52. Dr. Falkinham's declaration should be given little, if any, weight, however, because it is based only on a review of the specification and claims of the '338 patent, and did not consider the prosecution history of the '338 patent. Falkinham Decl., ¶ 4. Moreover, the Falkinham declaration is based on a factually incorrect allegation that use of specific primers is not disclosed in the '338 patent. Persing Decl., ¶ 13.

In contrast, Vysis submits herewith the declaration of its expert, Dr. David H. Persing, based on a full consideration of all of the intrinsic evidence, which the Federal Circuit has stated will in most instances alone resolve any ambiguity in a disputed claim term. *Vitronics*, 90 F.3d at 1583. Dr. Persing, after considering the claims, specification, and pertinent prosecution history of the '338 patent, disagrees with Dr. Falkinham and states that, in his opinion, the '338 patent claims include specific types of amplification. Persing Decl. ¶¶ 4, 6, 7, 19. Dr. Persing bases that opinion on (a) his belief that those of ordinary skill in the art as of December 21, 1987 reading the specification of the '338 patent would conclude that the term "amplify" as used in the claims of the '338 patent includes specific amplification, and (b) his review of the prosecution history of the '338 patent showing that both the patent owner and the patent examiners considered the invention to encompass specific amplification techniques such as PCR. Persing Decl. ¶¶ 8-18.

2. The Testimony Of The Patent Owner's Ex-Employees Should Be Given No Weight

Gen-Probe relies heavily on testimony of two former employees of Vysis' predecessor company Gene-Trak Systems -- Jon Lawrie, one of the inventors of the '338 patent, and Jim Richards, a business development person. According to the Federal Circuit, this testimony should be given little, if any, weight:

> [t]he **subjective intent** of the **inventor** when he used a particular term is of **little or no probative weight** in determining the scope of a claim **(except as documented in the prosecution history)**. . . . it is not unusual for there to be a significant difference between what an inventor thinks his patented invention is and what the ultimate scope of the claims is after allowance by the PTO.

Markman, 52 F.3d at 985.

Thus, the testimony of inventor Lawrie is simply irrelevant to the claim construction issue. Moreover, Gen-Probe relies on only some of Dr. Lawrie's testimony while ignoring other testimony. For example, Gen-Probe cites testimony from Dr. Lawrie that the '338 patent was directed to methods separate from PCR, but ignores Dr. Lawrie's testimony that he believed that the invention of the '338 patent "is not limited to nonspecific amplification." Banks Decl., Ex. H, p. 262, lns. 8-14.

Gen-Probe also relies heavily on a document authored by Jim Richards and testimony from Richards about that document purportedly relating to the invention of the '338 patent. This document and the Richards testimony are utterly irrelevant to the claim construction issue. First of all, Jim Richards is not even an inventor of the '338 patent, and in fact worked in business development. Moreover, at his deposition, Richards testified that at the time he authored the document Gen-Probe relies on, he had not even read the patent application that eventually issued as the '338 patent. Banks Decl., Ex. I, p. 184, lns. 7-9.

Accordingly, the testimony of these ex-employees should have no bearing on the proper interpretation of the '338 patent claims.

III. CONCLUSION

For the reasons pointed out herein, Gen-Probe's motion should be denied.

Date: May 25, 2001

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

Case No.: 99CV 2668H (AJB)

CERTIFICATE OF SERVICE

CERTIFICATE OF SERVICE

I, the undersigned, declare under penalty of perjury that I am over the age of eighteen years and not a party to this action; my business address is 4665 Park Blvd., San Diego, California 92116; and that I served the below-named persons the following documents:

VYSIS' OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

DECLARATION OF THOMAS W. BANKS IN SUPPORT OF VYSIS' OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

DECLARATION OF DR. DAVID H. PERSING IN SUPPORT OF VYSIS' OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

DEFENDANT'S STATEMENT OF DISPUTED FACTS IN OPPOSITION TO PLAINTIFF'S MOTION FOR PARTIAL SUMMARY JUDGMENT

NOTICE OF LODGMENT OF CASE AUTHORITY NOT IN OFFICIAL REPORTER SYSTEM IN SUPPORT OF DEFENDANT VYSIS' OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

in the following manner:

1. X By personally delivering copies to the person served.

2. _____ By leaving, during usual office hours, copies in the office of the person served with the person who apparently was in charge and thereafter mailing (by first-class mail, postage prepaid) copies to the person served at the place where the copies were left.

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4. _____ By placing a copy in a separate envelope, with postage fully prepaid, for each address named below and depositing each in the U.S. Mail at San Diego California on May 25, 2001.

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

DECLARATION OF THOMAS W. BANKS IN SUPPORT OF VYSIS' OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

I, Thomas W. Banks, declare and state as follows:

1. I have personal knowledge of the facts set forth in this declaration.

2. I am an attorney licensed to practice in the State of California and admitted to practice in the United States District Court for the Southern District of California. I am a partner at the law firm of Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P., and represent Defendant Vysis, Inc. ("Vysis") in this litigation.

3. Attached as Exhibit A to this declaration is a true and correct copy of United States patent application serial number 07/136,920, as filed on December 21, 1987, from the prosecution history of the '338 patent.

4. Attached as Exhibit B to this declaration is a true and correct copy of the July 20, 1990 Office Action (Paper No. 2) in application serial no. 07/136,920 from the prosecution history of the '338 patent.

5. Attached as Exhibit C to this declaration is a true and correct copy of the March 12, 1992 Office Action (Paper No. 2) in application serial no. 07/644,967 from the prosecution history of the '338 patent.

6. Attached as Exhibit D to this declaration is a true and correct copy of the November 5, 1992 Office Action (Paper No. 3) in application serial no. 07/944,505 from the prosecution history of the '338 patent.

7. Attached as Exhibit E to this declaration is a true and correct copy of the December 5, 1995 Preliminary Amendment and Response to Restriction Requirement (Paper No. 8) in application serial no. 08/238,080 from the prosecution history of the '338 patent.

8. Attached as Exhibit F to this declaration is a true and correct copy of the October 16, 1997 Notice of Allowability (Paper No. 23) in application serial no. 08/238,080 from the prosecution history of the '338 patent.

9. Attached as Exhibit G to this declaration is a true and correct copy of the January 16, 2001 Interview Summary (Paper No. 12) in the application for reissue of the '338 patent, serial no. 09/533,906.

10. Attached as Exhibit H to this declaration is a true and correct copy of page 262 of the transcript of the deposition of Jonathon Michael Lawrie taken February 15, 2001.

11. Attached as Exhibit I to this declaration is a true and correct copy of page 184 of the transcript of the deposition of James C. Richards taken March 30, 2001.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge and belief.

Executed this 24th day of May, 2001 at Palo Alto, California.

Thomas W. Banks

136920

PATENT APPLICATION SERIAL NO. _____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

050	01/07/88	136920	1	101	340.00 CK
050	01/07/88	136920	1	102	34.00 CK
050	01/07/88	136920	1	103	48.00 CK

PTO-1556
(5/87)

TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of U.S.S.N. 922,155, entitled TARGET AND BACKGROUND CAPTURE METHODS FOR AFFINITY ASSAYS, filed October 1986, and hereby incorporated by reference.

The present invention pertains to methods, reagents, compositions, kits, and instruments for use in capturing target molecules. In particular, the present invention relates to methods, reagents, compositions, and kits for capturing deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) from clinical samples. Embodiments of the present invention provide methods for rapid, sensitive detection of nucleic acid targets in clinical samples adaptable to non-radioactive labeling techniques and automation.

The following definitions are provided to facilitate an understanding of the present invention. The term "biological binding pair" as used in the present application refers to any pair of molecules which exhibit natural affinity or binding capacity. For the purposes of the present application, the term "ligand" will refer to one molecule of the biological binding pair and the term "antiligand" or "receptor" will refer to the opposite molecule of the biological binding pair. For example, without limitation, embodiments of the present invention have applications in nucleic acid hybridization assays where the biological binding pair includes two complementary strands of polynucleic acid. One of the strands is designated the ligand and the other strand is designated the antiligand. However, the biological binding pair may include antigens and antibodies, drugs, and drug receptor sites and enzymes and enzyme substrates.

The term "probe" refers to a ligand of known qualities capable of selectively binding to a target antili-

gand. As applied to nucleic acids, the term "probe" refers to a strand of nucleic acid having a base sequence complementary to a target strand.

The term "label" refers to a molecular moiety capable of detection including, by way of example, without limitation, radioactive isotopes, enzymes, luminescent agents, and dyes. The term "agent" is used in a broad sense, including any molecular moiety which participates in reactions which lead to a detectable response. The term "cofactor" is used broadly to include any molecular moiety which participates in reactions with the agent.

The term "retrievable" is used in a broad sense to describe an entity which can be substantially dispersed within a medium and removed or separated from the medium by immobilization, filtering, partitioning, or the like.

The term "support" when used alone includes conventional supports such as filters and membranes as well as retrievable supports.

The term "reversible," in regard to the binding of ligands and antiligands, means capable of binding or releasing upon imposing changes which do not permanently alter the gross chemical nature of the ligand and antiligand. For example, without limitation, reversible binding would include such binding and release controlled by changes in pH, temperature, and ionic strength which do not destroy the ligand or antiligand.

The term "amplify" is used in the broad sense to mean creating an amplification product which may include by way of example, additional target molecules, or target-like molecules which are capable of functioning in a manner like the target molecule, or a molecule subject to detection steps in place of the target molecule, which molecules are created by virtue of the presence of the target molecule in the sample. In the situation where the target is a polynucleotide, additional target, or target-like molecules, or molecules subject to detecting

can be made enzymatically with DNA or RNA polymerases or transcriptases.

Genetic information is stored in living cells in threadlike molecules of DNA. In vivo, the DNA molecule is a double helix, each strand of which is a chain of nucleotides. Each nucleotide is characterized by one of four bases: adenine (A), guanine (G), thymine (T), and cytosine (C). The bases are complementary in the sense that, due to the orientation of functional groups, certain base pairs attract and bond to each other through hydrogen bonding. Adenine in one strand of DNA pairs with thymine in an opposing complementary strand. Guanine in one strand of DNA pairs with cytosine in an opposing complementary strand. In RNA, the thymine base is replaced by uracil (U) which pairs with adenine in an opposing complementary strand.

DNA consists of covalently linked chains of deoxyribonucleotides and RNA consists of covalently linked chains of ribonucleotides. The genetic code of a living organism is carried upon the DNA strand in the sequence of the base pairs.

Each nucleic acid is linked by a phosphodiester bridge between the five prime hydroxyl group of the sugar of one nucleotide and the three prime hydroxyl group of the sugar of an adjacent nucleotide. Each linear strand of naturally occurring DNA or RNA has one terminal end having a free five prime hydroxyl group and another terminal end having a three prime hydroxyl group. The terminal ends of polynucleotides are often referred to as being five prime termini or three prime termini in reference to the respective free hydroxyl group. Complementary strands of DNA and RNA form antiparallel complexes in which the three prime terminal end of one strand is oriented to the five prime terminal end of the opposing strand.

Nucleic acid hybridization assays are based on the tendency of two nucleic acid strands to pair at comple-

mentary regions. Presently, nucleic acid hybridization assays are primarily used to detect and identify unique DNA or RNA base sequences or specific genes in a complete DNA molecule, in mixtures of nucleic acid, or in mixtures of nucleic acid fragments.

The identification of unique DNA or RNA sequences or specific genes within the total DNA or RNA extracted from tissue or culture samples may indicate the presence of physiological or pathological conditions. In particular, the identification of unique DNA or RNA sequences or specific genes, within the total DNA or RNA extracted from human or animal tissue, may indicate the presence of genetic diseases or conditions such as sickle cell anemia, tissue compatibility, cancer and precancerous states, or bacterial or viral infections. The identification of unique DNA or RNA sequences or specific genes within the total DNA or RNA extracted from bacterial cultures or tissue containing bacteria may indicate the presence of antibiotic resistance, toxins, viruses, or plasmids, or provide identification between types of bacteria.

Thus, nucleic acid hybridization assays have great potential in the diagnosis and detection of disease. Further potential exists in agriculture and food processing where nucleic acid hybridization assays may be used to detect plant pathogenesis or toxin-producing bacteria.

One of the most widely used nucleic acid hybridization assay procedures is known as the Southern blot filter hybridization method or simply, the Southern procedure (Southern, E., J. Mol. Biol.I, 98,503, 1975). The Southern procedure is used to identify target DNA or RNA sequences. This procedure is generally carried out by immobilizing sample RNA or DNA to nitrocellulose sheets. The immobilized sample RNA or DNA is contacted with radio-labeled probe strands of DNA having a base sequence complementary to the target sequence carrying a

radioactive moiety which can be detected. Hybridization between the probe and the sample DNA is allowed to take place.

The hybridization process is generally very specific. The labeled probe will not combine with sample DNA or RNA if the two nucleotide entities do not share substantial complementary base pair organization standard. Hybridization can take from three to 48 hours depending on given conditions.

However, as a practical matter there is always nonspecific binding of the labeled probe to supports which appears as "background noise" on detection. Background noise reduces the sensitivity of an assay. Unhybridized DNA probe is subsequently washed away. The nitrocellulose sheet is placed on a sheet of X-ray film and allowed to expose. The X-ray film is developed with the exposed areas of the film identifying DNA fragments which have been hybridized to the DNA probe and therefore have the base pair sequence of interest.

The use of radioactive labeling agents in conjunction with Southern assay techniques have allowed the application of nucleic acid assays to clinical samples. Radioactive decay is detectable even in clinical samples containing extraneous proteinaceous and organic material. However, the presence of extraneous proteinaceous and organic material may contribute to nonspecific binding of the probe to the solid support. Moreover, the use of radioactive labeling techniques requires a long exposure time to visualize bands on X-ray film. A typical Southern procedure may require 1 to 7 days for exposure. The use of radioactive labeling agents further requires special laboratory procedures and licenses.

The above problems associated with assays involving radioisotopic labels have led to the development of techniques employing nonisotopic labels. Examples of nonisotopic labels include enzymes, luminescent agents, and dyes. Luminescent labels emit light upon exitation by an

external energy source and may be grouped into categories dependent upon the source of the exciting energy, including: radioluminescent labels deriving energy from high energy particles; chemiluminescent labels which obtain energy from chemical reactions; bioluminescent labels wherein the exciting energy is applied in a biological system; and photoluminescent or fluorescent labels which are excitable by units of electromagnetic radiation (photons) of infrared, visual or ultraviolet light. See, generally, Smith et al., Ann. Clin. Biochem., 18: 253, 274 (1981).

Nonisotopic assay techniques employing labels excitable by nonradioactive energy sources avoid the health hazards and licensing problems encountered with radioisotopic label assay techniques. Moreover, nonisotopic assay techniques hold promise for rapid detection avoiding the long exposure time associated with the use of X-ray film.

However, nonisotopic assays have not conveyed the sensitivity or specificity to assay procedures necessary to be considered reliable. In luminescent assays, the presence of proteins and other molecules carried in biological samples may cause scattering of the exciting light or may absorb light in the spectrum of emission of the luminescent label, resulting in a quenching of the luminescent probe.

In enzymatic assays, the presence of proteins and other molecules carried in biological samples may interfere with the activity of the enzyme.

Similarly, in colorimetric assays, the change in color may not be detectable over proteins and other materials carried in biological samples.

Embodiments of the present invention are concerned with target and background capture on supports and on retrievable supports including magnetic particles. Magnetic particles have been suggested as supports for the synthesis of organic compounds, including oligomers such

as DNA, RNA, polypeptides, and other multiunit molecules that have a defined sequences. See, for example, European Patent Application No. 83112493.8 to Steven A. Benner and Genetics Institute. However, magnetic particles have not been suggested as retrievable supports for target capture and background removal.

Other utilization of magnetic particles has included magnetic fluids in the blood, R. Neubauer, IEEE transactions on magnetics MAG-9, 445 (1973); attachment of functional group for separation of biomolecules, U.S. Patent No. 3,970,518 to I. Giaver; labelling of cell-surface receptors, S. Margel et al., Jour. Imm. Meth. 28:341-53 (1979); attachment to drugs for magnetic targeting during therapeutic, A. Senyei et al., J., App. Phys., 49 (6): 3578 (1978), K. Wieder et al., Pro. Soc. of Exp. Bio. Med., 58:141 (1978), K. Mosbach and U. Shroeder, FEBS letters 102:112 (1979); selective separation of viruses, bacteria, and other cells, R. Molday et al., Nature 268:438 (1977); and incorporation of magnetic particles as support in gel affinity chromatography for biological polymers, K. Mosbach and L. Anderson, Nature 270:359 (1977), which are incorporated herein by reference.

The use of a two probe system to effect target capture on conventional non-retrievable supports has been suggested in an article authored by Ann-Christine Syuänen, Matti Laaksonen and Hans Söderlund entitled "Fast Quantification of Nucleic Acid Hybrids by Affinity-Based Hybrid Collection;" Nucleic Acids Research, 14(12): 5037 (1986).

SUMMARY OF THE INVENTION

It is an object of the present invention to provide methods, reagents, compositions, kits, and instrumentation for performing assays for target molecules of interest. Other objects will be presented hereinafter. For convenience, without limitation embodiments of the present invention can be grouped into areas of target

capture, background capture, and combinations thereof.

Turning first to target capture, an embodiment of the present invention feature capture and release cycles to isolate target molecules. The method includes contacting a sample medium potentially containing target molecules with probes and a first support associated or capable of associating with at least one probe under binding conditions. The probes are capable of selectively reversibly binding to the target molecule to form a complex including the probe target and the first retrievable support. Next, the support is separated from the sample medium and brought into contact with a second medium. Next, the support is subjected to releasing conditions to release the target from the support and the support is separated from the second medium. Next, a second support is contacted with the second medium under binding conditions. The second support is associated with or capable of associating with at least one probe capable of selectively binding to the target molecule. Under binding conditions, the target forms a complex with the probe associated to second support for further processing.

Preferably, the first support is retrievable in the sense that it is capable of substantially homogeneous dispersion within the sample medium and can be substantially physically separated, retrieved, or immobilized within the sample medium.

Separation of the first support from the first medium removes nonspecifically bound cellular debris attached to the first support. Further binding of the target molecule to a second support further concentrates the target for detection and permits further release-capture cycles for greater purification.

A further embodiment of the present method features a retrievable support. The method includes contacting the sample potentially carrying target nucleic acid with a retrievable support in association with a probe moiety.

The retrievable support is capable of substantially homogenous dispersion within a sample medium. The probe moiety may be associated to the retrievable support, by way of example, by covalent binding of the probe moiety to the retrievable support, by affinity association, hydrogen bonding, or nonspecific association.

The support may take many forms including, by way of example, nitrocellulose reduced to particulate form and retrievable upon passing the sample medium containing the support through a sieve; nitrocellulose or the materials impregnated with magnetic particles or the like, allowing the nitrocellulose to migrate within the sample medium upon the application of a magnetic field; beads or particles which may be filtered or exhibit electromagnetic properties; and polystyrene beads which partition to the surface of an aqueous medium.

A preferred embodiment of the present invention includes a retrievable support comprising magnetic beads characterized in their ability to be substantially homogeneously dispersed in a sample medium. Preferably, the magnetic beads carry primary amine or carboxyl functional groups which facilitate covalent binding or association of a probe entity to the magnetic support particles. Preferably, the magnetic support beads are single domain magnets and are super paramagnetic exhibiting no residual magnetism. The first probe includes a probe ligand moiety capable of specifically binding to antiligand under binding conditions. The retrievable support is capable of substantially homogeneous dispersion within the sample media and includes at least one antiligand moiety capable of binding to ligand under binding conditions to form a target-probe support complex. Next, the retrievable support and sample medium are separated to allow the sample medium to be processed further.

Embodiments of the invention are suitable for capturing target molecules from a clinical sample medium containing extraneous material. The order of contacting

the sample medium with probe or retrievable support is a matter of choice. However, the choice may be influenced by the kinetics of binding between the probe and target on one hand, and between the probe ligand and support antiligand on the other.

As applied to polynucleotide target molecules and homopolymer ligands and antiligands, the homopolymer ligand and antiligand binding is generally faster than probe binding to target. Probe binding to the target is sterically impaired after the probe ligand is bound to the support antiligand. A preferred embodiment includes contacting the sample medium with the reagent and bringing the mixture to hybridization conditions. Next, the retrievable support is dispersed in the reagent and sample medium allowing the formation of a target-probe complex in advance of the formation of probe support complexes.

A further embodiment of the present invention features a multiple probe system.

Preferably the method includes a reagent including a first probe as previously described and at least one second probe capable of binding to the target molecule and having label moieties capable of detection. The second probe is capable of forming a target (first and second) probe-support complex. The step of separating the retrievable support from the sample medium not only removes extraneous material from the target-(first and second) probe-support complex, but also separates any second probe which is not bound to the target. Second probe unbound to target contributes to background noises, false signals indicating the presence of target.

Further processing may include release of the target (first and second) probe complex from the retrievable support into a second medium and rebinding of the target (first and second) probe complex to new support. The first retrievable support may carry nonspecifically bound materials which can interfere with assay procedures.

Thus, after the release of the target-probe complex from the retrievable support and the retrievable supports removal, a second support having an antiligand moiety capable of binding to the probe ligand can be brought into contact with the target-probe complex under binding conditions to effect a further cycle of target-probe binding or capture for further purification and concentration of target-probe complex.

Further processing may include background capture. A further embodiment of the present invention includes a method wherein the second probe has a second ligand moiety. The method further includes a background support having a second antiligand moiety. The second ligand moiety and second antiligand moiety are capable of stably binding under binding conditions only when the second probe is unbound to the target molecule. The method further includes the step of contacting a medium potentially containing second probe unbound to target with a background support under binding conditions. Next, the background support is separated from the medium to remove unbound second probe reducing background noise.

The term "background support" is used in the conventional sense to include filters and membranes as well as retrievable supports. Binding to the background support does not need to be releasible.

A preferred retrievable support includes, by way of example without limitation, particles, grains, beads, or filaments capable of dispersion within and separation from a medium. Methods of separation include by way of example, without limitation, of filtration, centrifugation, precipitation, surface floatation, settling, or the introduction of electromagnetic fields.

The present method can be applied to polynucleotide target molecules. Preferably, the first and second probes bind quickly to a polynucleotide target "in solution" as opposed to the situation where either the target or probe is immobilized.

The retrievable support, capable of substantial dispersion within a solution, permits interactions between the retrievable support and probes which mimic "in solution" hybridization. In solution, hybridization can be completed in approximately 3-15 minutes. The rapid hybridizations and simplicity of the present methods permit automation. The present method allows nucleic acid sequences contained in clinical samples to be separated from extraneous material allowing the methods to be applied to nonisotopic labeling techniques.

An embodiment of the present method where the target molecule is a polynucleotide, includes contacting a sample medium with reagent under binding conditions. The reagent includes at least one first polynucleotide probe and at least one second polynucleotide probe. The first probe is capable of forming a complex with the target molecule and has a first homopolymer ligand moiety. The second probe is capable of forming a complex with the target molecule in addition to the first probe. The second probe includes a label moiety which has a second homopolymer ligand moiety which is different than the first homopolymer ligand of the first probe. Next, the reagent and sample medium are contacted with a background support and a target capture support. The background support includes at least one second homopolymer antiligand moiety capable of binding to the second homopolymer ligand moiety of the second probe when said second probe is unbound to target. The target capture support includes at least one first homopolymer moiety capable of binding to the first homopolymer ligand moiety of the first probe. The background support and the target capture support remove background noise and the target capture support further concentrates the target-(first and second) probe complex for further processing and separates the target-(first and second) probe complex from cellular debris. Further processing includes the detection of the label moiety indicative of the presence of

the target molecule.

Turning now more specifically to embodiments of the invention pertaining to background capture, one embodiment includes a method wherein probe and target are allowed to form a complex. Next, uncomplexed probe is brought into contact with a support under binding conditions. The support is capable of selectively binding unbound probe. Next, the support is separated from the probe-target complex.

A still further embodiment of the present invention includes a method of separating a plurality of target molecules for further processing.

One embodiment includes the sequential addition and removal of probes specific to target molecules on a plurality of supports. A further embodiment includes a method which includes contacting a sample with a first series probe and capturing the target and probe on a plurality of supports. The first series probe includes a ligand capable of association with the support. The first probe series includes probes for all plurality targets which are capable of binding to supports specific for each target molecule. The supports are capable of being separated from each other, the separation of which results in individual types of target molecules being isolated with the support.

A further embodiment of the present invention includes a reagent composition. The reagent composition includes a first probe and a second probe. The first probe is capable of forming a complex with a target molecule and includes a probe ligand moiety capable of specifically binding to antiligand under binding conditions. The second probe is capable of forming a complex with the target molecule and includes a label moiety capable of detection. The reagent composition can be used to capture and detect the target in a sample medium when used with a retrievable support having antiligand moieties.

A further embodiment of the present reagent composition includes a second probe having a second ligand moiety capable of stably binding to an antiligand only in the situation where the second probe is unbound to the target molecule. The reagent composition allows background noise to be reduced by contacting sample potentially containing an unbound second probe with a background support having a second antiligand moiety.

A further embodiment includes a support capable of substantially homogeneous dispersion in a sample medium having oligonucleotide antiligands adapted for binding to oligonucleotide ligands on probes.

A preferred embodiment of the support includes, by way of example, particles, grains, filaments, and beads capable of separation. Means of separation include, by way of example without limitation, precipitation, settling, floatation, filtration, centrifugation, and electromagnetism.

A preferred embodiment includes polystyrene beads, between 10-100 microns in diameter, which are capable of substantially homogeneous dispersion and separation from a medium by filtration or floatation. Another preferred embodiment includes ferromagnetic beads. A ferromagnetic bead marketed under the trademark BIO-MAG is capable of substantially homogeneous dispersion in an aqueous medium and can be retrieved or immobilized by an electromagnetic field. The ferromagnetic bead includes an iron core which is coated with an amine reactive covering. The beads are generally spherical and have a diameter of one micron. The polystyrene and ferromagnetic beads are treated to include antiligand moieties.

A further embodiment of the present invention includes a kit for performing assays for target molecules which are part of a biological binding pair. In the case where the target is a polynucleotide having a specific base sequence, the kit includes a reagent wherein the reagent includes a first polynucleotide probe and a

second polynucleotide probe. The first and second probes are capable of binding to mutually exclusive portions of the target to form a complex in which both probes are bound to the target. The first probe is capable of reversibly binding to a first support under binding conditions, and the second probe includes a label moiety capable of detection. The kit further includes a first support allowing the support to form complexes with the target and probes which can be selectively separated from the sample medium.

A further embodiment of the present kit includes a second probe and a background support. The second probe, when not bound to the target, is capable of selectively binding to a background support. The background support is capable of being separated from a medium containing reagent to remove the nonspecifically bound second probe.

A further embodiment of the present invention includes an instrument for performing assays in accordance with the present method. In the situation where the target is a polynucleotide, the instrument includes a reaction chamber adapted for receiving reagent and target in a substantially mixed homogeneous state. The reagent includes a first and a second polynucleotide probe. Each probe is capable of binding to mutually exclusive portions of the target forming a complex in which both probes are bound to the target. The first probe is capable of reversibly binding to a first support under binding conditions and the second probe includes a label moiety capable of detection. The instrument further includes means for contacting a first support with the reagent and sample to allow the first probe and target-probe complex to become bound to the support. The instrument further includes means for bringing the sample, reagent, and support to binding conditions to form target-probe complexes bound to support. The instrument further includes means for bringing the first probe into releasing conditions. Finally, the instrument

includes means for separating the support from the sample and from the reagent.

The term "reaction vessel" is used in a broad sense to include any means of containment including, by way of example without limitation, cuvettes, test tubes, capillaries, and the like.

Suitable means for bringing the sample, reagent, and support into binding conditions or bringing reagent and support into releasing conditions include by way of example, temperature controls which can elevate or lower the temperature of the sample, reagent, and support to selectively denature or anneal polynucleotide strands.

Suitable means for separating the support from the reagent or sample include by way of example, electromagnets for use in conjunction with magnetic beads, fibers affixed to an anchoring support, centrifuges for use with polystyrene grains, and the like.

Further embodiments of the present invention include means for bringing the reagent and target into contact with background support under binding conditions to remove any second probes having label moieties which second probes are not specifically bound to the target.

Embodiments of the present instrument adapted for use with luminescent label moieties include suitable label excitation means. Instruments for use with fluorescent label moieties include lasers or light emitting assemblies with filters to define appropriate wave lengths. Instruments for use with chemiluminescent label moieties include injection apparatus for injecting cofactors into the reaction chamber.

The invention also features a method for assaying a sample for a target polynucleotide, which sample contains the target polynucleotide and non-target polynucleotides, the method involving contacting the sample with a polynucleotide probe capable of forming a complex with the target polynucleotide, substantially separating the complex from the non-target polynucleotides in the sample,

amplifying the target polynucleotide, to form an amplification product, and measuring or detecting the amplified target polynucleotide. This method advantageously can be used in conjunction with the target capture and background capture steps described above.

Brief Description of the Drawings

Figs. 1-3 are flow diagrams illustrating steps, apparatus, and reagents used in methods of the invention. The term "Figure 1" refers collectively to Figure 1a and Figure 1b. Similarly, the term "Figure 2" refers collectively to Figure 2a and Figure 2b.

Figs. 4-6 are diagrammatic representations of capture amplification methods of the invention.

Fig. 7 is a diagram illustrating features of an apparatus made in accordance with one embodiment of the present invention.

Fig. 8 is a diagrammatic representation of a genetic construction used in the invention.

Detailed Description

Turning now to the drawings, which by way of illustration depict preferred embodiments of the present invention, and in particular Figure 1, a method of procedure, with necessary reagent compositions, is illustrated in schematic form for an assay for target polynucleotide strands. Conventional assay techniques include many target strands, and many probe strands would be used to perform an assay. However, for the simplicity to further an understanding of the invention, the illustration depicts only limited numbers of probes, support entities, and targets. Figure 1 features a method utilizing retrievable supports.

Step 1 of the assay illustrated in Figure 1 begins with a clinical sample which, by way of illustration, contains cells. The cells potentially carry target nucleic acid, either DNA or RNA, having a base sequence

of particular interest indicative of pathogens, genetic conditions, or desirable gene characteristics. The clinical samples can be obtained from any excreta or physiological fluid, such as stool, urine, sputum, pus, serum, plasma, ocular lens fluid, spinal fluid, lymph, genital washings, or the like. Individuals skilled in the art may desire to reduce biopsy samples to single cell suspensions or small clumps by means known in the art. For example, biopsy samples of solid tissues can be effectively reduced to single cell suspensions or to small clumps of cells by agitating the biopsy sample in a mixture of 0.5 M sodium chloride, 10 mM magnesium chloride, 0.14 M phosphate buffer, pH 6.8, and 25 Mg/ml cyclohexamide. Isolation of specific cell types by established procedures known in the art, such as differential centrifugation, density gradient centrifugation, or other methods, can also be applied at this step.

The cells are then treated to liberate their DNA and/or RNA. Chemical lysing is well known in the art. Chemical lysing can be performed with the dilute aqueous alkali, for example, 0.1 to 1.0 M sodium hydroxide. The alkali also serves to denature the DNA or RNA. Other denaturization and lysing agents include elevated temperatures, organic reagents, for example, alcohols, amides, amines, ureas, phenols and sulfoxides, or certain inorganic ions, for example chaotropic salts such as sodium trifluoroacetate, sodium trichloroacetate, sodium perchlorate, guanidinium isothiocyanate, sodium iodide, potassium iodide, sodium isothiocyanate, and potassium isothiocyanate.

The clinical sample may also be subjected to various restriction endonucleases to divide DNA or RNA into discrete segments which may be easier to handle. At the completion of the sample processing steps, the clinical sample includes sample nucleic acid, cellular debris, and impurities. In the past, sample nucleic acid was separated from cellular debris and impurities by nonspecific

binding of the nucleic acid to filters or membranes and washing cellular debris and impurities from the filter or membrane. However, in practice, some cellular debris and some impurities, as well as nontarget nucleic acid, are nonspecifically bound to the filter or membrane and are not removed by washes.

An embodiment of the present invention, as illustrated in Step 1, includes contacting the sample potentially carrying target nucleic acid with a retrievable support in association with a probe moiety. The retrievable support is capable of substantially homogenous dispersion within a sample medium. The probe moiety may be associated to the retrievable support, by way of example, by covalent binding of the probe moiety to the retrievable support, by affinity association, hydrogen binding, or nonspecific association.

The support may take many forms including, by way of example, nitrocellulose reduced to particulate form and retrievable upon passing the sample medium containing the support through a sieve; nitrocellulose or the materials impregnated with magnetic particles or the like, allowing the nitrocellulose to migrate within the sample medium upon the application of a magnetic field; beads or particles which may be filtered or exhibit electromagnetic properties; and polystyrene beads which partition to the surface of an aqueous medium.

A preferred embodiment of the present invention includes a retrievable support comprising magnetic beads characterized in their ability to be substantially homogeneously dispersed in a sample medium. Preferably, the magnetic beads contain primary amine functional groups which facilitate covalent binding or association of a probe entity to the magnetic support particles. Preferably, the magnetic support beads are single domain magnets and are super paramagnetic exhibiting no residual magnetism.

The particles or beads may be comprised of magnetic particles, although they can also be other magnetic metal or metal oxides, whether in impure, alloy, or composite form, as long as they have a reactive surface and exhibit an ability to react to a magnetic field. Other materials that may be used individually or in combination with iron include, but are not limited to, cobalt, nickel, and silicon. Methods of making magnetite or metal oxide particles are disclosed in Vandenberghe et al., "Preparation and Magnetic Properties of Ultrafine Cobalt Ferrites," J. of Magnetism and Magnetic Materials, 15 through 18: 1117-18 (1980); E. Matijevic, "Mono Dispersed Metal (Hydrous) Oxide--A Fascinating Field of Colloidal Science," Acc. Chem. Res., 14:22-29 (1981), the disclosures which are incorporated herein by reference.

A magnetic bead suitable for application to the present invention includes a magnetic bead containing primary amine functional groups marketed under the trade name BIO-MAG by Advanced Magnetics, Inc. A preferred magnetic particle is nonporous yet still permits association with a probe moiety. Reactive sites not involved in the association of a probe moiety are preferably blocked to prevent nonspecific binding of other reagents, impurities, and cellular material. The magnetic particles preferably exist as substantially colloidal suspensions. Reagents and substrates and probe moieties associated to the surface of the particle extend directly into the solution surrounding the particle. Probe moieties react with dissolved reagents and substrates in solution with rates and yields characteristic of reactions in solution rather than rates associated with solid supported reactions. Further, with decreasing particle size the ratio of surface area to volume of the particles increases thereby permitting more functional groups and probes to be attached per unit weight of magnetic particles.

Beads having reactive amine functional groups can be reacted with polynucleotides to covalently affix the

polynucleotide to the bead. The beads are reacted with 10 percent glutaraldehyde in sodium phosphate buffer and subsequently reacted in a phosphate buffer with ethylenediamine adduct of the phosphorylated polynucleotide in a process which will be set forth in greater detail in the experimental protocol which follows.

Returning now to Step 2, the retrievable support with associated probe moieties is brought into contact with the clinical sample and, progressing through to Step 3, is brought into binding conditions. The probe moiety specific for the target of interest becomes bonded to the target strands present in the clinical sample. The retrievable support, dispersed throughout the sample and reagent medium, allows the probe moieties and target to hybridize as though they are free in a solution.

Hybridizations of probe to target can be accomplished in approximately 15 minutes. In contrast, hybridizations in which either the probe or target are immobilized on a support not having the capability to be dispersed in the medium may take as long as 3 to 48 hours.

Extraneous DNA, RNA, cellular debris, and impurities are not specifically bound to the support. However, as a practical manner, a small amount of extraneous DNA, RNA, cellular debris, and impurities are able to and do in fact nonspecifically bind to any entity placed within the reaction vessel including the retrievable support. Embodiments of the present invention facilitate the further purification of clinical samples to remove extraneous DNA, RNA, cellular debris, and further impurities from target polynucleotides.

Step 4 of Figure 1 depicts the separation of the support of the clinical sample and the suspension of the support into a second medium. The second medium thus includes the retrievable support with the associated probe bound to target polynucleotide strands. Also carried with the retrievable support is extraneous DNA, RNA,

cellular debris, and impurities nonspecifically bound to the support, but in a much lower concentration than what was initially found in the clinical sample. Those skilled in the art will recognize that some undesirable materials can be reduced by washing the support prior to suspension in the second medium.

The retrievable support with associated probe and target strands suspended in the second medium is subject to further denaturation as set forth in Step 5 thereby allowing the target to disassociate from the probe moieties of the retrievable support. The denaturation process may or may not release nonspecifically bound extraneous DNA, RNA, cellular debris, or impurities from the retrievable support. However, Step 5 of the present method allows the retrievable support to be removed from the second medium carrying with it much of the nonspecifically bound cellular debris, impurities, and extraneous DNA, and RNA initially carried over from the first clinical sample medium.

As set forth in Step 6, a new support can be introduced into the second medium under binding conditions to again capture target polynucleotide strands on probe moieties associated with the retrievable support. It will be recognized by those skilled in the art that the new support may actually include the original retrievable support after recycling steps to further purify and remove nonspecifically bound DNA, RNA, cellular debris, and impurities. Thus, the only impurities present in the second medium include DNA, RNA, cellular debris, and impurities previously nonspecifically bound to the support which has subsequently been released from the first support and dissolved or suspended in the second medium.

However, such impurities can be further removed from the target polynucleotides by removing the second retrievable support from the second medium and again repeating the cycle of introducing the retrievable support into a further medium, denaturation, and removal of

the old support. Those skilled in the art will recognize that the magnetic beads described in the present invention are susceptible of being raised out of a solution or being held in place as a solution is removed or added to a containment vessel.

The ability of the magnetic beads to participate in the reactions which mimic "insolution kinetics" strands allow the completion of a cycle of denaturation and binding to the target to be accomplished in three to fifteen minutes.

After sufficient purification and concentration, the target can be detected by luminescent or radioactive methods known in the art as indicated in Step 8. Purification of the medium containing the target allows the detection of nonisotopic label moieties without cellular debris and impurities.

Turning now to Figure 2, which features a multiple probe method, a further embodiment to the present assay method is illustrated beginning with a clinical sample containing polynucleotide target which is processed in accordance with the clinical sample of the previous figure with the introduction of solubilizing agents and reagent. The reagent of the assay method depicted in Figure 2 includes a first polynucleotide probe strand (P_1) and a second polynucleotide probe strand (P_2) capable of forming a complex with the target in which both probes (P_1 and P_2) are bound to the target. The first probe (P_1) is capable of associating with a retrievable support (S_1) under binding conditions. The second probe has at least one label moiety capable of detection. The label moiety is illustrated in the drawings with an asterisk or a star. Following the introduction of solubilizing agents and reagent under denaturation conditions, the solution containing the clinical sample potentially includes target polynucleotides and reagent in the form of the first and second probes, plus cellular debris, solubilizing agents, impurities, and

extraneous RNA and DNA.

Under binding conditions as illustrated in Step 2, the first and second probes (P_1 and P_2) bind to mutually exclusive portions of the target. The hybridization of the probes (P_1 and P_2) to the target in solution is rapid and unimpaired by association with a solid support. In order to insure the binding of the target to the first and second probe strands (P_1 and P_2) an excess of probe is employed. However, even if an excess of probe (P_1 and P_2) were not employed, some probe would fail to find target and would remain unhybridized in the sample medium. The unhybridized second probe (P_2) having a label moiety constitutes background noise if present during detection.

The first probe (P_1) is capable of binding to a support (S_1) by means of a ligand capable of binding to an antiligand moiety on a support. The ligand (L_1) includes, by way of example, a tail portion comprising a homopolymer. The support (S_1) includes an antiligand (A_1) capable of receiving and binding to ligand (L_1). The antiligand (A_1) includes, by way of example, a homopolymer complementary to the ligand (L_1) of probe (P_1).

Turning now to Step 3, under binding conditions the antiligand moiety (A_1) of support (S_1) associates or binds to the ligand moiety (L_1) of the first probe (P_1) which is itself bound to the target and linked to the second probe (P_2). The support may take many forms. Beads or particulate supports can be dispersed in solution and participate in binding with target probe reactions which demonstrate near in solution kinetics. Further, retrievable beads and particulate supports can separate probe-target complexes from nondissolvable debris without clogging problem inherent in more conventional filters or membranes.

However, conventional membranes, filters, or cellulose supports may also be employed for some applications in which clogging may not be a problem. Due to the rapid

hybridization of the probes to target insolution, a solid nonbead or nonparticulate membrane or filter support can be incorporated into the reaction vessel. The solution of reagent and sample can be passed through the support to affect target capture. The support (S_1) is illustrated in Figure 2 as a retrievable support.

In solution with the target-probe support complex are unbound first and second probe moieties, unbound target solubilizing agents, impurities, and cellular debris. The unbound second probe (P_2) which has label moieties constitutes noise, producing a signal which mimics the presence of target. A small amount of extraneous cellular debris, solubilizing agents, impurities, and probes may also become nonspecifically bound to the retrievable support.

In Step 4, the support (S_1) is separated from the clinical sample medium. If a retrievable support is used, separation can be accomplished either by immobilizing the retrievable support within a reaction vessel or by withdrawing the retrievable support from the sample medium directly. Those skilled in the art will recognize that the immobilized support can be washed to reduce undesirable material.

Turning now to Step 5, the target-probe support complex is substantially free of extraneous RNA, DNA, solubilizing agents, impurities, and cellular material and can be monitored for the presence of the label moieties indicative of the presence of the target molecule. However, a small amount of extraneous DNA, RNA, solubilizing agents, impurities, and cellular materials may still be nonspecifically bound to the support (S_1). Moreover, unbound, in the sense that it is not associated with target, second probe (P_2) may also be nonspecifically bound to the support (S_1) and can affect signals from nonisotopic label moieties. The presence of unbound second probe moiety (P_2) having label moieties is a significant cause of background noise thereby reducing the

accuracy of the assay procedure.

Thus, as an alternative Step 5, the first support (S_1) may be suspended into a second medium where the support (S_1) is separated from the target-probe complex by denaturation.

Following denaturation, in Step 6, the first support (S_1) is removed from the second medium and replaced with a second support (S_2). The second support (S_2) includes an antiligand moiety (A_1) capable of binding to the ligand moiety (L_1) of the first probe.

Moving to Step 7, under binding conditions, the target-probe complex reassociates with the second support (S_2). The removal of the first support (S_1) removes extraneous material, debris, and probes nonspecifically bound to the first support (S_1) from the assay medium.

As illustrated in Step 8, the medium containing the target-probe complex can be monitored for the presence of the labels. However, further purification of the assay medium can be performed to further reduce the presence of background and extraneous materials which may have been carried from the sample medium nonspecifically bound to the first retrievable support (S_1) and subsequently dissolved or disassociated from the first support (S_1) into the second medium.

Thus, the second retrievable support (S_2) may be brought into contact with a third medium, the medium brought into conditions to release the target-probe complex from the support, and the support removed to complete a further cycle. The number of cycles will be a matter of choice depending on the type of sample, type of label moieties, and the sensitivity of the detection equipment. Different types of supports may be used at different times. Thus, a retrievable support can be used to gather or concentrate the target-probe complexes from sample mediums or solutions initially to avoid problems of clogging typical of membranes or filters. The second or third supports preferably includes a membrane or

filter with antiligand moieties (A_1) which bind to the ligand moiety (L_1) of the first probe (P_1). Membrane or filter supports can simplify process steps allowing flow-through recovery of target-probe complexes.

A further embodiment of the present invention is particularly well suited for reducing background noise. Referring now to Figure 3, a modification of the previous assay procedure illustrated in Figure 2 is described. In Figure 3, a target polynucleotide has formed a complex with a first and second probe moiety (P_1 and P_2) similar to the probe moieties described in Figure 2. However, the second probe includes a second ligand (L_2). The second ligand (L_2) may include, by way of example, a single terminal ribonucleotide which complexes with a borate antiligand, an alternating copolymer which binds with a complementary copolymer, a biotin ligand which binds to an avidin antiligand, or as illustrated, homopolymer ligand (L_2), and a complementary homopolymer antiligand (A_2).

Turning now to Step 1, a background support capable of selectively binding to the second probe (P_2), only when it is not bound to a target, is brought into contact with the medium containing the target-probe complex. The medium further includes free, disassociated first and second probes (P_1 and P_2). The labeled second probe (P_2), which contributes to the background noise, is specifically bound to the background support (B_1) by a vast molar excess of antiligand moieties (A_2) associated with the background support (B_1). Following binding of the unbound labeled probe (P_2) to the background support (B_1), the background support (B_1) is removed from the medium as illustrated in Step 2. The medium containing the target-probe complex can be monitored for the presence of the label contained upon the second probe (P_2) with a reduction in background noise. Alternatively, the medium containing the target-probe complex can be subjected to further processing.

The further processing can include further background reduction by repeating Steps 1 through 3 described in Figure 3 or, steps previously described in conjunction with Figure 2. For example, background reduction steps can be incorporated into the processing of a clinical sample as illustrated in Figure 2 at any point in which the ligand and antiligand moieties of the first and second probes do not interfere, and the target is complexed with the first and second probes.

An embodiment of the present method can practiced with additional amplification steps to generate an amplification product to improve the sensitivity of the assay. Turning now to Figures 4, 5, and 6 , each Figure includes a Step 1 wherein target is captured with the use of a capture probe and a retrievable support in the form of a bead. The polynucleotide target includes areas defined as a^1, b^1, and c^1. The polynucleotide probe includes an area, "a" capable of binding to its complement "a^1" of the target. The probe further includes a ligand capable of binding to an antiligand associated with the bead. As illustrated, the ligand of the probe and the antiligand of the bead are complementary homopolymers.

In Step 2 of Figures 4, 5, and 6, the target is separated from extraneous polynucleotides, impurities, cellular material, and solubilizing reagents from sample processing procedures.

In Step 3 of Figures 4, 5, and 6, the isolated target is non-specifiably amplified to form a multitude of amplification products.

Figure 4, Step 3, depicts amplification of the target DNA to form an amplification product subject to detection, complementary RNA, through the enzyme, core RNA polymerase. In Figure 4, Step 1, the capture probe is complexed or coated with recA protein to facilitate probe target binding. Core RNA polymerase forms RNA complementary to the DNA target template. As the enzyme reads through the target sequences, the RNA probe area

"a" and subsequent new mucleotide sequences are removed from the target which is able to bind to new recA coated probes to form a multitude of RNA polynucleotides having an area "c" which can be detected. The integer "n" represents a plurality of amplification products.

In the situation where the target is RNA, such as ribosomal RNA (rRNA) or messenger RNA (mRNA) the target RNA can be replicated nonspecifically by denaturing the RNA and subjecting the RNA to an enzyme such as Qβ replicase or reverse transcriptase.

Figure 5 illustrates the application of a two enzyme amplification system. In Step 3(a) of Figure 5, DNA polymerase is used in conjuntion with hexamer primers to generate DNA segments which are complementary to the target. In Step 3(b), core RNA polymerase is used to form additional RNA complements to both target DNA and DNA target complements.

Figure 6 illustrates the application of an enzymatic amplification system based on the enzyme DNA polymerase. Thus, in step 3(a), the target, separated from extraneous polynucleotides, impurities and debris, is subjected to DNA polymerase in conjunction with non-specific hexamer primers. The DNA polymerase generates DNA segments which are complementary to the initial target. The new DNA product, formed from the target DNA, is also a substrate for replication. The target and complements are subjected to cycling steps to denature the target and target complements and to add new enzyme to create new copies of the target and the target complement.

Following formation of the enzyme product, Step 4 of Figures 4-6 illustrates capture of the target and/or enzyme product as previously described with a further probe and support. The target and/or enzyme reaction product are amenable for further process steps including detection.

An embodiment of the present methods may be practiced with an aid of apparatus set forth in schematic

form in Figure 7. The apparatus includes the following major elements: at least one containment vessel, means for controlling the association of a probe with a target molecule and a retrievable support, means for separating the retrievable support from a sample solution, and means for releasing the target molecule from the retrievable support. These major elements may take various forms and are described more fully below.

The apparatus will be described below for illustration purposes as applying the methods described in Figures 2 and 3 relative to a target molecule which includes a polynucleotide. Thus, at Station 1, a clinical sample is placed within the containment vessel with solubilizing agents such as chaotropic salts, enzymes, and surfactants in order to dissolve cellular material and release nucleic acids. The containment vessel may include agitation elements to facilitate the break up of cells. The containment vessel may include any type of vessel, tube, cuvette suitable for containing the sample.

In an instrument designed for automated analysis, the apparatus set forth in Figure 7 will preferably include means for receiving a plurality of containment vessels. For illustration purposes, the containment vessels containing the sample are analyzed sequentially. Thus, containment vessels are conveyed to a first station and then to subsequent stations where various steps of the assay method are performed.

The various stations are linked by conveying means. Conveying means may include a rotatable turntable, conveying belt, or the like. As applied in a clinical hospital setting, conveying means may include manual movement. Thus, hospital staff may obtain a tissue sample from a patient and place the sample in the containment vessel. Sample processing, including the breakup of the tissue sample and initial mixing of solubilizing agents and reagents would be initiated at bedside and continued as the containment vessel traveled to a subsequent sta-

tion for further processing. References to stations are for illustration purposes. Those skilled in the art will recognize that certain stations or steps may be combined or reversed.

Returning now to the first station, sample and solubilizing agents are placed within a containment vessel in which an agitation element thoroughly mixes the sample and solubilizing agents, releasing nucleic acids from cellular materials. Conveying means carry the containment vessel to Station 2 where the containment vessel receives reagent.

The reagent includes a first polynucleotide probe and a second polynucleotide probe. The first and second probes are capable of forming a complex with the target polynucleotides in which both probes are bound to mutually exclusive portions of the target. The first probe is also capable of binding to a retrievable support under binding conditions. The second polynucleotide probe includes a label moiety capable of detection. The reagent and sample nucleic acid are denatured by a heating element and conveyed to Station 3.

At Station 3, the containment vessel receives a first support depicted by open circles. The first support is homogeneously dispersed within the sample medium by suitable means including an agitation element. Examples of suitable supports include, without limitation, polystyrene beads, magnetic beads and other particulate or filamentous substances. As illustrated, the first support includes a magnetic bead having polynucleotide antiligands of deoxythymidine (dT). The first probe includes a tail portion of deoxyadenosine (dA) capable of binding to the first support during binding or hybridization conditions.

Moving to Station 4 hybridization conditions are imposed upon the sample medium by cooling by a cooling element. However, those skilled in the art will recognize that means to alter salt concentrations can be

readily substituted for thermal controls. Thus, the target polynucleotide forms a complex with the first and second probes. Further, the homopolymer deoxyadenosine (dA) tail portion of the first probe hybridizes to the deoxythymidine (dT) homopolymer of the retrievable support.

From Station 4, the containment vessel is moved to Station 5 where the retrievable support is immobilized on the wall of the containment vessel by activating a magnetic element. If polystyrene beads were substituted for magnetic beads, the polystyrene bead would be immobilized by filtering or density differences. The sample medium is disposed of carrying with it most of the extraneous DNA, RNA, solubilizing agents, cellular material, and impurities. The immobilized retrievable support is washed to further remove extraneous DNA, RNA, solubilizing agents, cellular materials, and impurities.

Further, although it is illustrated that the retrievable support is immobilized on the wall of the reaction vessel, it is also possible to remove the retrievable support from the reaction vessel by a magnetic element and dispose of the first reaction vessel containing with it extraneous DNA, RNA, solubilizing agents, and cellular material which may be nonspecifically bound to the reaction vessel walls.

The retrievable support is placed in a second medium, either the same containment vessel or a new containment vessel. The containment vessel, containing the retrievable support in a second medium is carried to Station 6.

At Station 6, the second medium is brought to denaturization conditions by suitable means including a heating element. The denaturization process releases the target-first and second-probe complex from the (dT) homopolymer of the retrievable support. The first support, potentially carrying extraneous DNA, RNA, impurities, and cellular material, is removed from the second medium. If

desired, amplification steps may be applied to the target, now substantially free of impurities, debris, and non-target polynucleotides. Amplification steps may include the generation of an amplification product with enzymes such as, by way of example, DNA polymerase, RNA polymerase, transcriptases, or Qβ replicase. In the event the amplification product is not the target molecule, the second probe is directed to the amplification product as well as a third capture probe which takes the place of the first probe. A background support is then brought into contact with the second medium and passed to Station 7.

At Station 7 a cooling element brings the second medium to hybridization temperatures. The background support includes a second antiligand capable of specifically binding to a ligand carried upon the second probe. For example, without limitation, a terminal nucleotide of the second probe can be synthesized to be a ribo derivative which specifically binds to borate moiety carried upon the second support. The second probe bound to the target as part of a probe target complex will not bind to the borate carried upon the third support due to stearic hindrances. However, unbound second probe will specifically bind to the borate support. Alternatively, the second probe may include a homopolymer such as deoxycytosine (dC) which binds to a deoxyguanine (dG) homopolymer linker on a second support. The length of the homopolymers are designed such that complexes of the target-first and second probes with the second support are not stable; however, complexes of the second probe alone with the second support are stable within reaction parameters. Indeed, background capture binding of background support to unbound second probe can be irreversible.

Next, the containment vessel containing the second medium and the background support is conveyed to Station 8 where the background support having second probe strands unbound to the target-probe complex is separated

from the second medium. Separation of the background support removes nonspecific background noise from the medium.

As illustrated, background capture is effected upon beads. However, those skilled in the art will recognize that the initial purification of the target-first and second probe complex from the clinical sample, removes all or most solid debris allowing background capture on filter or membrane supports through which the second medium can be flushed.

From Station 8, the purified medium containing the target-probe complex with reduced background is conveyed to Station 9. At Station 9, a third support, depicted as a membrane or filter, is brought into contact with the second medium which is brought to hybridization temperatures by a heating element. The third support includes first antiligand moieties which bind to the first ligand moieties of the first probe, or if an amplification product is generated in previous steps, to a first ligand moiety of a third probe directed to the amplification product. Thus, if the first ligand moiety of the first probe is of a homopolymer of deoxyadenosine (dA), the third support may include homopolymer of deoxythymidine (dT). As illustrated, the third support includes filters or membranes through which the second medium can be flushed; however, beads or particles may also be used. The third support serves to further concentrate the target-first and second probe complex and permits further reduction of background and interfering materials which do not specifically bind to the third support. Moving to Station 10, the third support concentrates the target-first and second probe complex allowing detection of label moieties carried upon the second probe.

The present invention is further described in the following typical procedures and experimental examples which exemplify features of the preferred embodiment.

I. Procedures

A. Materials

All reagents were of analytical grade or better. Magnetic beads marketed under the trademark BIO-MAG containing functional amino groups were obtained from Advanced Magnetics, Inc. of Cambridge, MA.

In the present example, all labeled nucleotides were obtained from New England Nuclear. The enzyme terminal deoxynucleotidyl transferase (TDT) was obtained from Life Sciences, Inc., St. Petersburg, Florida. The oligonucleotide pdT_{10} was obtained from Pharmacia PL Biochemicals.

B. Synthesis of Probes

The following sets forth typical protocols and methods. Referring now to Figure 8, two probes were constructed to the sense strand of the enterotoxin gene elt A1 of Escherichia coli, in accordance with the constructional map, Figure 8, of Spicer, E. K. and J. A. Noble, 1982, J. of Biological Chem. 257, 55716-55751.

One set of probes was synthesized beginning at position 483 of the gene sequence and extending onward 30 nucleotides in length, hereinafter referred to as the A483 probe. A second probe was synthesized beginning at position 532 in the gene sequence and extending 30 nucleotides in length, hereinafter referred to as the A532 probe. A third probe was synthesized beginning at position 726 in the gone sequence and extending 39 nucleotides in length, hereinafter referred to as the A726 probe. The specific base sequences (5' to 3') are set forth in Table 1 below:

Table I

Probe	Sequence
A483	AGA CCG GTA TTA CAG AAA TCT GAA TAT AGC
A532	AGA TTA GCA GGT TTC CCA CCG GAT CAC CAA
A726	GTC AGA GGT TGA CAT ATA TAA CAG AAT TCG GGG GGG GGG

The probes were synthesized by methods available in the art. The numbering system is adapted from the 768 nucleotide sequence available through Intelligenetics sequence bank ECO ELT A1.

Of the ten G residues at the 3 prime end of probe A726, three guanine bases towards the 5' end are capable of binding to three complementary cytosine bases of the tox gene. Stretches of three cytosines are common in DNA. The ten guanine bases form a ligand capable of binding to a poly C antiligand carried upon a support such as oligo dC-cellulose. However, seven guanine bases will not form a stable association with a support at 37°C, particularly if the probe is bound to target due to steric hindrance and the size of the target-probe complex. Probe A726 was modified by the random addition of approximately three residues of ^{32}P-dC and ^{32}P-dG to its 3' end with terminal transferase.

Those skilled in the art will recognize that other probes can be readily synthesized to other target molecules.

C. Preparation

The target in Example Nos. 1, 2 and 3 is the enterotoxin gene elt A1. The enterotoxin gene elt A1 is carried as part of the plasmid EWD-299 obtained from Stanford University.

In Example No. 1, enterotoxigenic bacteria were grown to log-phase in Luria broth. The enterotoxigenic bacteria were lysed and the plasmid EWD-299 isolated.

The plasmid EWD-299 was further digested with the restriction enzymes Xba 1 and HIND III. A fragment of 475 base length was used as a target and purified by electro-elution from a 1 percent agarose gel. In order to follow the efficiency of capture steps, the fragment was 5' end labeled with ^{32}P-ATP with the enzyme polynucleotide kinase following manufacturer's instructions.

In Example Nos. 2 and 3, the enterotoxigenic bacteria and wild type nonenterotoxigenic E. coli JM83 were separately grown to log phase. The wild type E. coli serves as a control. Separate extracts of enterotoxigenic bacteria and wild type bacteria were prepared by substantially solubilizing the cells in chaotropic solutions. Thus, the bacteria cultures, in Luria broth, were added to solid guanidinium thiocyanate (GuSCN) to a concentration of 5M GuSCN, Tris-HCl to a concentration of 0.3M, and EDTA (pH7) to a concentration of 0.1M. The chaotropic-bacterial solutions were then heated to 100°C for five minutes and cooled. The resultant enterotoxigenic bacteria extract was serially diluted with wild type nonenterotoxigenic bacteria extract. The concentration of tox plasmids per cell and the cell number in the extracts were measured by conventional techniques. The original extracts solubilized in GuSCN contained approximately 10^9 enterotoxigenic E. coli per ml and 100 plasmids/cell.

D. Synthesis of Beads

Retrievable supports were prepared from magnetic beads. Other retrievable supports include particles, fibers, polystyrene beads or other items capable of physical separation from a medium. Magnetic beads were synthesized with an adduct of deoxythymidine of ten base length to allow the beads to associate with probes tailed with deoxyadenosine in a readily reversible manner.

Thus, 100 ml of beads having amine functional groups such as BIO-MAG (M4100) beads were washed four times with

20 mM sodium phosphate (pH 6.7) in four 275 ml T-flasks. The beads were then washed with 1% glutaraldehyde in 20 mM sodium phosphate. Next, the beads were reacted in 100 ml of 10 percent glutaraldehyde in 20 mM sodium phosphate (pH 6.7) for three hours at room temperature. The beads were then washed extensively with 20 mM sodium phosphate (pH 6.7) and then washed once with 20 mM phosphate (pH 7.6).

Separately, a purified ethylene diamine (EDA) adduct of pdT_{10} (EDA-dT_{10}) was prepared in accordance with Chu, B.C.F., G. M. Wahl, and L. E. Orgel; Nucleic Acid Res. 11, 6513-6529 (1983) incorporated by reference herein. The concentration of EDA-dT_{10} was adjusted to 1 OD/ml in 20 mM phosphate (pH 7.6).

The EDA-dT_{10} was combined with the magnetic beads to allow the EDA-dT_{10} to react with the free aldehyde groups of the beads. The mixture of EDA-dT_{10} and beads was divided into a plurality of 50 ml polypropylene tubes. The tubes containing the reaction mixture and beads were placed in a tube rotator and agitated overnight at room temperature.

Next, the beads were washed five times to remove noncovalently bound EDA-dT_{10} with a wash solution of sterile 20 mM phosphate (pH 6.7) in large 275 ml T-flasks and diluted to 200 ml with the wash solution.

For storage, beads can be maintained for months in a buffer of 20 mM phosphate, to which is added sodium azide to 0.1% and SDS to 0.1%. Bead preparations are stored at 4°C protected from light.

The beads were then prehybridized to block nonspecific binding sites in a buffer, hereafter referred to as "prehybridization buffer", of 0.75 M sodium phosphate (pH 6.8), 0.5% sodium lauroyl sarcosine, 10 micrograms/ml E coli DNA, 0.5 milligram per milliliter mg/ml bovine serum albumin (BSA) (Nuclease-free) and 5 mM ethylenediaminetetraacetic acid) (EDTA). Before applying the probes and beads to target capture procedures, two prehy-

bridizations of the beads were performed. The prehybridization procedure included placing the beads in ten volumes prehybridization buffer.

The first prehybridization procedure was performed with agitation at 60°C. The second prehybridization procedure was performed at room temperature with swirling. A 0.1 percent isoamyl alcohol solution was added to the solutions as a defoamant.

The binding capacity of dT_{10}-derivatized beads was measured by the following procedure. In separate vessels, dT_{50} and dA_{50} were 5' end labeled with ^{32}P-dT and ^{32}P-dA respectively to a specific activity (Sa) of about 10^6 dpm/microgram. Next, the Sa was accurately measured for a known quantity of reacted dT_{50} by trichloroacetic acid precipitation.

Next, 5 µg of $^{32}P\text{-}dA_{50}$ and 5 µg of $^{32}P\text{-}dT_{50}$, having substantially identical Sas of between 100,000-200,000 dpm/mg, were separately added to tubes containing prehybridization buffer and brought to a volume of 1 ml.

A known sample volume of prehybridized beads was placed into four tubes. Two of the four tubes each receive 0.5 ml of the $^{32}P\text{-}dA_{50}$ mixture and the remaining two tubes receive 0.5 ml of the $^{32}P\text{-}dT_{50}$ mixture. All four solutions are brought to hybridization conditions for five minutes. The beads are thereafter immobilized and washed. The activities of the solutions are then monitored. The total binding capacity, C, for a quantity of bead preparation measured in micrograms is set forth below:

$$C = V(A - T)/X$$

In the above equation X is the specific activity of $^{32}P\text{-}dT_{50}$ in cpm/mg, V is the volume ratio of total volume to sample volume, A is the average activity of the beads suspended in ^{32}P-dA solutions in cpm, and T is the average activity of the beads suspended in ^{32}P-dT solutions in cpm.

Those skilled in the art will recognize that other beads, particles, filaments, and the like can be formulated with other nucleotide combinations or homopolymers. For example, polyA-derivized beads were produced by substituting (for the purified EDA adduct of dT_{10}) a solution containing 100 mg poly A (mw>100,000) in 50 ml of 20 mM sodium phosphate (pH7.6).

E. Target Capture Procedures

Bead preparations were used to capture target polynucleotides. The following sets forth a typical experimental target capture protocol demonstrating retrievable supports and reversible captures for purposes of illustration, without limitation, the procedure will be discussed using a first probe A483 and a second probe A532. The first probe, A483, was randomly 3' end labeled with ^{32}P-dCTP and ^{32}P-dGTP to a specific radioactivity of about 10^{10} dpm/mg. The second probe, A532, was tailed with about 70 unlabeled dA residues by the enzyme terminal transferase.

First, 200 µg/ml of labeled probe A483 an 400 µg/ml of tailed probe A532 were mixed with varying amounts of a heat-denatured 475 mer Xba 1-HIND III restriction fragment of the enterotoxin gene at 65°C for 15 minutes in 1.4M sodium chloride.

Next, target capture was initiated by contacting the medium containing the target and probe moieties with an aliquot of dT_{10}-magnetic beads having 3 micrograms/ml of dA_{50} binding capacity following prehybridization procedures to reduce nonspecific binding to the magnetic bead. The magnetic bead and the probe-target complex was incubated at room temperature in 0.1 ml prehybridization buffer in 5 ml polypropylene tubes for two to five minutes.

The tubes were placed into a Corning tube magnetic separator. The Corning tube magnetic separator upon activation imposes a magnetic field through the polypro-

pylene tubes which immobilizes the magnetic beads on the inner walls of the tubes. During the time that the magnetic beads are immobilized on the side walls of the polypropylene tubes, the original medium was removed and discarded.

While immobilized, the beads were washed three times with 0.6 ml of prehybridization buffer containing isoamyl alcohol as a defoamant. Following the addition of the prehybridization buffer, the beads were resuspended by removing the tubes from the magnetic field and by subjecting the medium to vigorous vortexing.

Next, the magnetic field was reapplied to immobilize the beads allowing the prehybridization buffer to be removed and discarded. The cycle of adding the prehybridization buffer, resuspending the beads, immobilizing the beads, and discarding the prehybridization buffer was repeated twice. Target-probe complexes held on the beads are available for further processing including additional steps of detection, background capture or further cycles of target capture.

A preferred target capture procedure includes release of the target-probe complex and recapture on a second support. Preferably the support is chemically distinct from the first support.

Release of the target-probe complex is effected in the following typical protocol. After the removal of the last prehybridization buffer, prehybridization buffer was added to the tube containing the beads. The beads were incubated with agitation at 60°C for one-two minutes to release the probe-target complexes from the bead. The magnetic separator was again activated with the temperature at 60°C and the eluate, containing free target-probe complexes, is removed from the tube. The eluate can be recaptured on additional retrievable supports or subjected to final capture on conventional supports. It will be recognized by those skilled in the art that the capture and release of the target probe complex from ret-

rievable supports such as the magnetic beads of the present example can be repeated as often as desired to reduce hybridization backgrounds.

Final capture of the probe-target complex was typically performed on nitrocellulose filters or nylon membranes containing nonspecifically bound or covalently bound dT-3000. Thus, the target-probe complexes carried upon the magnetic beads were released from the magnetic beads by heating the beads to 60°C in prehybridization buffer for two minutes. The beads were immobilized and the eluate removed and passed through a 0.2 micron acrodisc (Gelman) to remove magnetic fines. The nitrocellulose filter containing dT-3000 selected, bound, and captured the dA tail on the unlabeled probes.

The use of a chemically different solid support for the final capture of the target-probe complex avoids binding background molecules which may have a high affinity for previously used supports. By way of illustration, it is possible for lower level contaminants with a natural high affinity for a particular support to repeatedly bind and elute with a support along with probe-target complexes. Such low level contaminants cannot be diluted out by repeated use of a retrievable support of the same composition as completely as by exposing them to supports of very different compositions. Low level contaminants can also be lowered by utilizing chemically distinct means to release the target-probe complexes from supports and recapture.

F. Background Capture Procedures

Background capture procedures permit the selective reduction of background noise permitting the detection of true signal indicative of the presence of target. Background capture can be applied in a single probe system or in systems using more than two probes. For example, in background capture procedures featuring a single probe,

the probe includes a label moiety and a ligand. The probe is capable of binding to a target and the ligand is capable of forming a stable bond to a support only when the probe is unbound to target.

Similarly, by way of example, background capture procedures featuring multiple probes in conjunction with target capture include two probes. A first target capture probe, having an unlabeled ligand capable of binding to a first support is used to capture the target and a second background capture probe, having a label moiety capable of detection includes a second ligand capable of binding to a second background support. Background capture is a valuable supplement to target capture for enhancing the signal to noise data of an assay.

The following sets forth a typical background capture protocol using a first target capture probe A532 and a second background capture probe A726 and a target enterotoxin gene elt A1. Those skilled in the art will recognize that the probes used for demonstration purposes are merely a matter of choice. Other probes could be used also.

The probe A532 was tailed with approximately 100 dA residues capable of reversibly binding to dT_{10} covalently linked magnetic beads for initial target capture and dT_{3000} nonspecifically bound to nitrocellulose for a final target capture. The probe A726 was end labeled with the random addition of approximately three residues of ^{32}P-dC and ^{32}P-dG to the 3' end with terminal transferase. The probe A726 is capable of binding to dC-cellulose when the probe is not hybridized to target.

A solution containing the target-first and second-probe-complex and potentially containing unbound second probe is mixed with dC-cellulose and the temperature of the mixture maintained at 37°C. The temperature, 37°C, is higher than the dissociation temperature of dG_7 with oligo dC, preventing binding of the target-first and second- probe-complex to the dC-cellulose. The temperature

is also lower than the dissociation temperature of dG_{10} with oligo dC to promote binding of unbound second probe having a dG tail to the dC-cellulose. Additionally, the target-first and second probe complex is sterically hindered to a greater degree in its approach to the dC-cellulose support than unbound second probe. The dC-cellulose containing the second probe A726 is removed by centrifugation, however, those skilled in the art will appreciate that other methods such as filtration may be used as well. The remaining eluate contains target-first and second probe complexes and a reduced concentration of unbound labeled second probe A726.

G. Examples

Individuals skilled in the art will recognize that the typical protocols for retrievable support preparation, probe preparation, target capture and background capture are capable of modification to suit special needs and purposes. The following examples incorporate the typical procedures outlined above unless otherwise noted.

Example 1

Target Capture and Assay Using Magnetic Bead

A target capture assay was performed with two probes and a magnetic bead retrievable support. The target included the Xba 1-Hind III fragment of the enterotoxigenic gene elt A1. A first probe included an A532 thirtimer oligonucleotide probe which was tailed with 130 unlabeled dA residues capable of binding to the dT_{10} residues of the magnetic beads support. A second probe included an A483 thirtimer oligonucleotide probe capable of binding to the same target 20 nucleotides downstream from the site of hybridization of the first probe. The second probe was labeled by tailing the thirtimer oligonucleotide with ^{32}P-dCTP and ^{32}P-dGTP to a specific radioactivity of 10^{10} DPM/microgram.

The tailed first probe and the labeled second probe were incubated at 65°C for 15 minutes in 1.4 M sodium chloride with various quantities of heat denatured 475mer restriction fragments of the tox gene. As a nonspecific binding background control, the tailed first probe and labeled second probe were incubated in identical solutions in the absence of any target. As specific binding controls, two additional reaction mixtures were formed. One reaction mixture included the tailed first probe and the unlabeled second probe incubated with four micrograms of denatured E. coli DNA, and a second reaction mixture of the tailed first probe and the labeled second probe incubated in ten micrograms of denatured human DNA in identical reaction mixtures without any target DNA.

After a 15 minute hybridization period, the samples were incubated for five minutes with dT-derivatized magnetic beads in 0.7 milliliters of 0.75 molar phosphate buffer (pH 6.8). The beads were magnetically immobilized and washed extensively as described previously. The target-probe complex was eluted from the beads at 60°C in 0.6 milliliters of 0.20 molar phosphate buffer (pH 6.8). The first set of beads was separated from the eluate and the target probe complex. A second group of magnetic beads was added to the eluate and brought to binding conditions to capture the target and probe complex again. The second set of beads was washed and the target again eluted from the beads and the beads separated from the eluate.

A third set of beads was added to the eluate containing the target-probe complex and placed under binding conditions to allow the beads to once again capture the target-probe complex. The beads were then washed extensively and the target eluted from the beads as previously described. The beads were then separated from the eluate and the eluate passed through dT_{3000}-nylon into two millimeter square slots, capturing the target-probe complex.

The dT_{3000} nylon membrane was prepared in which 2 µg dT_{3000} was covalently bound to nylon using a hybri-slot apparatus (Betlesda Research Laboratory). Briefly, dT_{3000} (Life Sciences) was dotted directly onto a nylon membrane such as Gene-Screen^{Tm} (New England Nuclear) in a salt-free Tris buffer. The membrane was dried at room temperature for 10 minutes, and then dried under an infrared lamp for an additional 10 minutes before cooling back to room temperature for another 10 minutes. The filter apparatus containing the nylon membrane was inverted on a uv-transilluminator (Fotodyne) and exposed to uv light for two minutes at 40uW/cm^2 to cross-link the dT_{3000} to the filter.

The dT_{3000} membrane was prehybridized by sequentially passing the following solutions through the membrane:

(1) 1% SDS;

(2) 0.5 mg/ml BSA in 0.5% SDS; and, finally,

(3) prehybridization buffer

The dT_{3000}-nylon potentially containing the target-probe complex was washed with 0.2 molar sodium phosphate and 5 millimolar EDTA. The nylon support was monitored overnight by audioradiography for the presence of the ^{32}P label moieties of the second probe. Following audioradiography, the bands were cut out of the filter and counted in base scintillation fluid. The counts were 2100 and 1400 counts per minute in the solution containing three femtomoles (10^{-15}moles) of a restriction fragment containing the tox gene. Samples containing 30 attomoles (10^{-18}moles) of the restriction fragment containing the tox gene produced a count of 62 counts per minute.

A third sample containing no DNA produced seven counts per minute. A fourth sample containing ten micrograms of heat denatured human DNA produced 0 counts per minute. A fifth solution containing 4 micrograms of heat denatured E. coli DNA produced 7 counts per minute. The absolute sensitivity of the protocol was estimated to be

10^{-18} mole of tox gene. The overall efficiency of the recovery of labeled target-probe complex was estimated to be 1 to 2 percent of the input. The assay demonstrated good specificity. There is no more labeled probe in the samples containing human DNA or E. coli DNA than in the sample containing no DNA at all. Repetition of the experimental protocol has produced overall efficiency of capture of the target of almost 5 percent. The procedures reduced background from an initial level of 10^{11} molecules of the labeled unhybridized probes to about 10^{4} moles. The reduction and background represents a 7 log improvement which more than adequately compensates for the reduction and efficiency of capture.

Example 2

The present example features target capture with background capture. Target and background capture was effected using an unlabeled first target capture probe, A532 as described in target capture, and a second labeled background capture probe A726.

First, 160 ng/ml dA-tailed A532 and 40 ng/ml ^{32}P-labeled probe A726 were combined to form a probe mix. The probe mix was added to 5 µl of bacterial extract containing various amounts of enterotoxigenic gene. The extract-probe mix was incubated at 22°C for 15 minutes.

After a fifteen minute hybridization period, the samples were diluted with ten volumes of prehybridization buffer incubated for five minutes with dT-derived magnetic beads in 0.7 ml of .75M phosphate buffer (pH 6.8) to effect target capture. The beads were magnetically immobilized and washed extensively. The target-first and second probe complex was eluted from the first support as previously described and the first solid support removed.

Next, the eluate containing the target-first and second-probe-complex and potentially containing unbound second probe was mixed with dC-cellulose and the temperature of the mixture maintained at 37°C. The temperature

37°C is higher than the dissociation temperature of dG_7 with oligo dC to prevent binding of the target-first and second- probe-complex to the dC-cellulose. The temperature was also maintained lower than the dissociation temperature of dG_{10} with oligo dC to promote binding of unbound second probe having a dG_{10} tail to the dC-cellulose. The target-first and second probe complex is sterically hindered to a greater degree in its approach to the dC-cellulose support than unbound second probe. The dC-cellulose was removed by centrifugation, however, those skilled in the art will appreciate that other methods such as filtration may be used as well.

The remaining eluate was passed through a 0.2 micron acrodisc (Gelman) to remove magnetic and cellulose fines. Then, the eluate was passed through nitrocellulose filters containing dT_{3000} at 22°C. The nitrocellulose effected final target capture.

Table 2 sets forth below the application of background capture:

Table 2

Step	Signal (CPM)	Noise (CPM)
First Experiment		
Before Target Capture	(unknown)	200,000
After Target Capture	1058	231
After Background Capture	495	25
After Filtration	395	<1
Second Experiment		
Before Target Capture	(unknown)	400,000
After Target Capture	1588	642
After Background Capture (Filtration step was not performed)	1084	69

The removal of noise to less than 1 cpm allows the detection of very small quantities of target within a sample. As little as 10^{-18} moles of target have been detected which is within the range necessary for clinical applications.

One round of target capture removed about 3 logs of background. One round of background capture removed 1 log of background not already removed by the primary target capture. Final target capture by filtration (a second round of target capture) removed 2 logs of background not removed by either of the first two steps. Target and background capture methods work <u>independently</u> to reduce backgrounds by about 6 logs in this example. Background capture appears to work better when applied after a first target capture. Apparently, background capture is much more sensitive to impurities in the sample than target capture.

The combination of background capture following target capture produces a greater benefit than either applied alone.

Although the foregoing examples recite radioactive label moieties, it is expected that the present procedure would have its greatest impact on assay procedures utilizing nonradioactive label moieties. In particular, the present invention would be applicable to luminescent label moieties including fluorescent and chemiluminescent agents. Suitable fluorescent labels include, by way example without limitation, fluoroscein, pyrene, acridine, sulforhodamine, eosin, erythrosin, and derivatives thereof. Suitable chemiluminescent agents include, by way of example without limitation, microperoxidase, luminol, isoluminol, glucose oxidase, acridinium esters and derivatives thereof.

<u>Example 3</u>

The following example features nonradioactive label moieties and multiple rounds of target capture from

spiked biological media. The spiked biological media resembles samples which would be obtained clinically in a medical setting.

Cell extracts of enterotoxigenic E. coli and wild type E. coli were prepared as previously described. To measure the sensitivity of the detection of tox genes in an environment analogous to a clinical setting, extract containing toxigenic bacteria was diluted with the extract containing the wild type E. coli as previously described.

The following materials were obtained from anonymous donors: human stool sample, cow's milk, human saliva, human phlegm, human whole blood, human serum, human urine and human semen. Clinical-type samples were solubilized over a time period of ten minutes. The stool sample, due to its solid nature, was solubilized in a solution of 5 M GuSCN, 0.3 M Tris-HCl (pH 7.4), 0.1 M EDTA (pH 7), 1% betamercaptoethanol. Following solubilization, aliquots of the sample were made and each aliquot was spiked with a known quantity of either toxigenic E. coli or wild type E. coli. The mixture was then passed through a crude filtration (Biorad Econocolumn) and heated to 100°C for five minutes.

The remainder of the samples were more liquid in nature and were handled differently than stool. Liquid samples were added to solid GuSCN to make the final concentration 5M. The solid GuSCN also contained sufficient Tris-HCl, EDTA, and betamercaptoethanol to make the final concentrations the same as in the stool example. Next, aliquots of the samples were made and each aliquot was spiked with a known amount of toxigenic E. coli or wild type E. coli. The mixture was passed through a crude filtration (Biorad Econocolumn and heated to 100°C for five minutes.

The preparation of probes in Example 3 differs from previous examples. A first capture probe was generated with the plasmid pBR322. The plasmid was restricted with

Hha I and Hae III and plasmid fragments were tailed with about 100 dA residues with terminal transferase. The target plasmid contains extensive homology with pBR322 (Spicer and Noble, J.Biol.257: 5716-21). Thus, first capture probes were generated from multiple fragments of both strands of the plasmid pBR322 in relatively large quantities.

A second label probe was made to combine specifically to the target enterotoxin gene. The second label probe was generated from an EcoRI-Hind III restriction fragment of the elt A1 gene cloned into bacteriophage M13mp18. The E. coli HB101 was infected with the bacteriophage and grown to midlog phase. The E. coli were harvested, and the bacteriophage were isolated. Bacteriophage was nick-translated with biotinylated dCTP (Enzo Biochemicals) using a stock nick-translation kit available from Bethesda Research Laboratories. Approximately five percent of the nucleotides were replaced with biotinyl nucleotides to form a biotin-labeled second probe.

A probe mix was made by combining 8 µg/ml of the second M13-tox probe with 4 µg/ml of the first dA-tailed first probe in 20mM Tris-HCl (pH 7.4) and 2mM EDTA. The probe mix was heated to 100°C for ten minutes to denature the probes.

One volume of the probe mix was mixed with one volume of sample of the dilution series to form a hybridization mixture. The hybridization mixture was maintained under hybridization conditions at 57°C for fifteen minutes. The hybridization mixtures were subsequently diluted with ten volumes of blocking buffer (0.75M sodium phosphate, pH 6.8, 0.5% sodium lauryl sarcosine, 10 mg/ml E. coli DNA, 0.5 mg/ml bovine serum albumin (BSA-nuclease free) and 5mM EDTA). To the hybridization mixture were added dT_{10} derivized magnetic beads prepared as previously described. Hybridization conditions were maintained approximately one minute at 22°C. The beads were then separated from the hybridization mixture by magneti-

cally immobilizing the beads. The beads were washed twice during a fifteen minute time interval to remove impurities in the biological specimen and unhybridized biotin labeled second probe.

Next, in a time period of approximately one minute, the first and second probe-target complex was eluated from the magnetic beads at 65°C in blocking buffer. The eluate and the first beads were separated.

In a time period of approximately seven minutes, the first and second probe-target complex was releasibly bound to a second set of beads and again released. A second set of dT_{10} derivized beads were then added to the eluate and hybridization conditions maintained for approximately one minute at 22°C. The beads were then washed and resuspended in blocking buffer. The bead blocking buffer mixture was then brought to 65°C to release the first and second probe-target complex.

Over a time period of five minutes, final capture of the first and second probe-target complex on nitrocellulose was effected. The eluate from the second beads was filtered through a Gelman acrodisc (0.2 micron). The eluate containing the first and second probe-target complex was then passed through a dT_{3000} nitrocellulose filter (prehybridized with blocking buffer) at 22°C.

In a time period of approximately thirty minutes the filter was further processed to detect the biotin labels of the second probe. Buffer compositions used in detection are identified below in Table 3.

Table 3
Detection Buffers

Buffer Number	Composition
1	1 M NaCl, 0.1 M Tris-HCl (pH 7.4), 5 mM $MgCl_2$, 0.1% Tween-20
1a	No. 1 with 5 mg/ml BSA, 10 micrograms/ml *E. coli* DNA
2	No. 1 with 5% BSA, 0.5% Tween-20
3	0.1 M NaCl, 0.1 M Tris-HCl (pH 9.5), 50 mM $MgCl_2$

First, the filter carrying the first and second probe-target complex, was incubated for approximately five minutes in detection buffer No. 2. Next, the filter was incubated for five minutes in a 1:200 dilution of strepavidin-alkaline phosphatase (Bethesda Research Laboratories) in detection buffer No. 1a. Thereafter, the filter was washed three times in one minute in detection buffer No. 1 and then washed twice in one minute in detection buffer No. 3.

Next, 5-Bromo-4-chloro-3-indolyl phosphate (BCIP) and nitroblue tetrazolium (NBT) (Kierkegaard and Perry) were diluted twelve times in detection buffer No. 3, and filtered through a 0.2 micron acrodisc. The diluted BCIP and NBT solution was added to the filter and color allowed to develop for fifteen minutes at 37°C.

Next, the filter was incubated in 50 mM Tris-HCl (pH 7.4) and 10 mM EDTA for one minute to stop the reaction. Sensitivity was determined visually on the filter or by densitometric scanning on a CS 930 (Shimadzu Scientific).

The steps in the present method are outlined below in Table 4.

Table 4
Elapsed Time

Step Number	Time Required (min.)	Cumulative Timed (min.)
1. Dissolution of biological sample; denaturation of DNA	10	10
2. Add labeled and unlabeled probes; hybridize in solution at 57°C	15	25
3. Capture probe-target complex on magnetic beads	1	26
4. Wash magnetic beads to remove impurities in the biological specimen and hybridization backgrounds	15	41
5. Elute the probe-target complex	1	42
6. Repeat steps 3-5 on a second set of beads (except abbreviate the washes)	7	49
7. Bind the probe-target complex to dT_{3000}-nitrocellulose	5	54
8. Incubate filter in blocking buffer	5	59
9. Bind streptavidin-alkaline phosphatase	5	64
10. Wash	5	69
11. Add dyes to detect enzyme	15	84
12. Quench reaction	1	85

Although Table 4 set forth an example wherein the elapsed time is just over one hour, the procedure is capable of modification and can be performed in shorter times. Nonradioactive probe assays of comparable sensitivity may require twelve hours to several days and require extensive sample preparation.

The sensitivity of the present assay is set forth in Table 5 below:

Table 5

Sensitivity Level

Biological Specimen	Concentration in the Hybridization Mixture	Number of Bacteria
bacterial extract alone		1500
human stool	2.5% (w/v)	2000
cow's milk	12.5% (v/v)	3000
human saliva	12.5% (v/v)	3000
human urine	12.5% (v/v)	9000
human semen	2.5% (v/v)	9000
human blood	12.5% (v/v)	9000
human serum	12.5% (v/v)	9000
human phlegm	12.5% (v/v)	9000

Further, the present procedures are capable of further modifications to improve sensitivities. For example, a combination of thermal elution and chemical elution in multiple captured release cycles produces a signal to noise ratio five times better than single forms of elution, either multiple thermal elutions alone or multiple chemical elutions alone.

Applying the same releasing or elution procedure tends to release the same background from the support. However, applying different releasing conditions tends to retain background on the support that would otherwise be eluted. It is unlikely that background will behave identically to target under two physically or chemically distinct conditions.

A typical chemical elution of target-probe complexes on magnetic beads includes bringing beads in contact with 3M GuSCN for one minute at room temperature. Examples of thermal elutions have been described previously.

The ability to detect bacteria would also be improved by directing probes to ribosomal RNA sequences. Ribosomal RNA sequences present a thousand fold increase in target per cell as compared to genomic DNA and clinically significant plasmid DNA.

The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by non-specific replication using standard enzymes (polymerases and/or transcriptases). After replication, the amplified nucleic acid can be reacted as above with capture probe, reporter probe, and capture beads to purify and then detect the amplified sequences.

In addition, where amplification is employed following purification of the target nucleic acids as described above, the amplified nucleic acids can be detected according to other, conventional methods not employing the capture probe, reporter probe, and capture beads described above, i.e., detection can be carried out in solution or on a support as in standard detection techniques.

Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ non-specific enzymes or primers (i.e., enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence). Although any background, non-target, nucleic acids are replicated along with target, this is not a problem because most of the background nucleic acids have been removed in the course of the capture process. Thus no specially tailored primers are needed for each test, and the same standard amplification reagents can be used, regardless of the targets.

The following are examples of the method.

Example 4:

The following example illustrates the use of RNA polymerase to amplify target DNA captured by a method which is a variation of the capture method discussed above.

Referring to Fig. 4, target DNA of a sample is first reduced in size by shearing or by limited nuclease digestion, according to standard methods. A recA protein coated capture probe is then added to the digested target DNA (Proc. Natl. Acid. Sci. U.S.A. (1986) 83:9591) The recA protein coated probe contains a nucleic acid sequence (a) that is homologous to a first target (a^1) sequence of the target DNA, as well as a homopolymer sequence homologous to a nucleic acid sequence on a capture bead. This capture bead is then added to the mixture to isolate and purify the target nucleic acid, as described above.

The captured DNA is amplified by treatment of the mixture with E. coli RNA polymerase lacking sigma subunit, i.e., core enzyme; E. coli RNA polymerase is described by R. Burgess in RNA Polymerase, Cold Spring harbor press, pp. 69-100, and can be purchased from New England Biolabs, Beverly, MA. The sigma subunit is removed according to the procedure described in J. Biol. Chem. (1969) 244:2168 and Nature (1969) =221=:43. Other phage or bacterial RNA polymerases that lack transcriptional specificity can also be used. Core enzyme is added together with nucleotide triphosphates and a low salt transcription buffer such as described in Eur. J. Biochem. (1976) 65:387 and Eur. J. Biochem (1977) 74, 1107.

A suitable nucleotide triphosphate/transcription buffer solution has the following composition:

0 to 50 mM NaCl or KCl
25 mM Tris HCl pH 7.9 buffer
10 mM $MgCl_2$
0.1 mM EDTA
0.1 mM dithiothreital

0.5 mg/ml BSA
0.15 mM UTP, GTP, CTP, ATP

The resulting non-specific transcription of the target DNA produces many RNA transcripts of the target DNA which are then captured using a capture probe containing a sequence (b^1) homologous to a sequence (b) of the RNA transcripts. A reporter probe containing a sequence (c^1) homologous to another sequence (c) of the RNA transcript is then used for detection.

Example 5

In this example both non-specific replication of target DNA and transcription of that DNA are used to amplify captured target DNA.

Referring to Fig. 5, denatured sample DNA is captured as described above and the enzyme DNA polymerase (for example, Klenow fragment; Dur. J. Biochem, (1974) 45:623 available from New England Biolabs), random oligohexamer primers (i.e., Hexamers prepared to contain randomly selected bases at each nucleotide position in the hexamer) and deoxynucleotide triphosphates are added in appropriate buffers to cause replication of target DNA to form additional double stranded DNA. Suitable oligohexamer primers are available under catalog No. 27-2166 from Pharmacia, Inc. Piscotaway, NJ. A suitable deoxynucleotide triphosphate/buffer solution has the following composition:

66 mM glycine-NaOH buffer, pH 9.2
6 mM $MgCl_2$
1 mM 2-mercaptoethonal
30 mM each d CTP, d GTP, d TTP, d ATP

Because the primers are random, some will, simple as a matter of statistics, bind to and cause replication of sample sequences, no matter what those sequences are. (Alternatively, the double stranded DNA can be formed by synthesis starting from capture probe a.) RNA polymerase lacking sigma subunit is then added along with nucleotide triphosphates and low salt transcription buffer. Tran-

scription from the target DNA (which has been increased in number) produces many RNA copies of this DNA. The RNA transcripts are then captured and detected as in example 4.

Example 6

In this example target DNA is replicated using DNA polymerase.

Referring to Fig. 6, sample DNA is denatured, reduced in size and captured as described in examples 4 and 5. DNA polymerase, for example, Klenow fragment, and deoxynucleotide triphosphates are added in appropriate buffer with random hexamer oligonucleotides to bring about non-specific double-stranded DNA syntheses. The *in vitro* synthesized DNA product is then made single stranded by heat treatment (e.g., 100°C for three minutes), or its equivalent, and additional DNA polymerase is then added to replace that rendered inactive by the heat treatment. Further *in vitro* DNA replication then is allowed to occur. The heat treatment and polymerization reactions are repeated about 10 times to produce an approximately 1,000-fold increase in the level of target DNA. The replicated DNA is denatured *in vitro* using heat or alkali and then captured and detected as described previously.

Example 7

In this example, rRNA or RNA transcribed from target DNA is purified using a capture probe, described above. The hybrid duplex is then denatured and single stranded nucleic acids are then replicated non-specifically using Qβ replicase (methods in Enzymology (1979) 60:628. This replicase replicated both messenger RNA and ribosomal RNA non-specifically under the conditions described by Blumental, Proc. Natl. Acad. Sci. U.S.A. 77:2601, 1908. Because the replication product is a template for the enzyme, the RNA is replicated exponentially.

While preferred embodiments have been illustrated and described, it is understood that the present inven-

tion is capable of variation and modification and, therefore, should not be limited to the precise details set forth, but should include such changes and alterations that fall within the purview of the following claims.

We Claim:

1. A method of amplification of target polynucleotide molecule potentially contained in a sample with non-target polynucleotides comprising the steps of:

a. contacting the sample potentially containing the target with a first support capable of specifically associating with the target under binding conditions.

b. separating said first support from the remaining sample to form a removal product which in the presence of target includes target;

c. subjecting said removal product to amplification which in the presence of target forms an amplification product.

2. The method of Claim 1 wherein said method further includes the step of determining the presence of said amplification product.

3. The method of Claim 2 wherein said step of determining the presence of said amplification product includes contacting said amplification product with a probe having a label moiety.

4. The method of Claim 1 wherein said method further includes the step of contacting said amplification product with a second support capable of specifically associating with said amplification product under binding conditions.

5. The method of Claim 1 wherein said first support includes a retreivable support.

6. The method of Claim 5 wherein said first support is capable of associating with the target through a probe.

7. The method of claim 6 wherein said probe includes a ligand capable of binding to an antiligand associated with said first support.

8. The method of Claim 6 wherein said probe is coated with recA protein.

9. The method of claim 1 wherein said amplifying step comprises treating said target with a polymerase.

10. The method of claim 9 wherein said polymerase is RNA polymerase, Qβ replicase, transcriptase or DNA polymerase.

11. The method of claim 9 wherein said target is DNA and, prior to said step of treating said target with said polymerase, said target is caused to replicate by subjecting said target to DNA polymerase and non-specific oligonucleoide primer.

12. The method of Claim 1 wherein said target is mRNA.

13. A method of amplifying target polynucleotide molecules potentially contained in a sample with non-target polynucleotides, said method comprising:

a) contacting said sample with a first polynucleotide probe under binding conditions, said first probe capable of specifically associating with said target under binding conditions to form a first probe-target complex;

b) substantially separating said first probe from said non-target polynucleotides in said sample to form a removal product which in the presence of target includes the first probe-target complex;

c) subjecting said removal product to amplification to form an amplification product the generation of which is dependent on the presence of target.

14. The method of claim 13 wherein said amplification product is detectable with a labeled probe.

15. The method of claim 13 further comprising the step subjecting said removal product and said amplification product, if present, to contact with a second probe under binding conditions said second probe capable of specifically associating with said amplification product to form a second probe-amplification product complex, said second probe capable of associating or in associa-

tion with a support to capture said amplification product for further processing.

16. The method of claim 15 wherein said further processing includes the steps of contacting said removal product and said amplification product, if present, with a label probe under binding conditions, said label probe capable of specific association with said amplification product under binding conditions, monitoring said amplification product for the presence of the label probe indicating the presence of the target molecule.

17. The method of claim 13 wherein said amplification comprises contacting said removal product with polymerase.

18. The method of claim 17 wherein said polymerase is RNA polymerase, Qβ polymerase, reverse transcriptase or DNA polymerase.

19. The method of claim 17 wherein said target polynucleotide is DNA and, prior to said step of treating said removal product with said polymerase, said target DNA is caused to replicate by subjecting said removal product to the enzyme DNA polymerase and non-specific oligonucleotide primer.

20. The method of claim 13 wherein said target polynucleotide is mRNA.

21. A kit for capturing and amplifying a target polynucleotide contained in a sample medium potentially containing the target with non-target polynucleotides comprising:

a) a first probe capable of binding to a retrievable support and said target under binding conditions;

b) a retrievable support capable of forming a substantially homogeneous dispersion within a sample medium and capable of separation therefrom to form a removal product which in the presence of target in the sample includes said target; and

c) amplification reagents adapted to be applied to said removal product.

22. The method of claim 21 wherein said retrievable support includes at least one bead.

23. The method of claim 22 wherein said bead is capable of interacting with a magnetic field.

24. An instrument for performing assays for target polynucleotides comprising :

a reaction chamber adapted for receiving target polynucleotides and non-target polynucleotides in a sample medium and a support capable of a substantially homogeneous dispersion within the sample medium and capable of forming a complex with the target;

means for separating the support from the sample medium to form a removal product, which in the presence of target in the medium includes target, which removal product is substantially free of non-target polynucleotides;

means to amplify said target as part of a removal product to form an amplification product; and

means to detect said amplification product.

ABSTRACT

A method of assay for target polynucleotides includes steps of isolating target polynucleotides from extraneous non-target polynucleotides, debris, and impurities and amplifying the target polynucleotide.

Declaration

As a below named inventor and petitioner in the foregoing petition, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS

the specification of which

(check one)

[X] is attached hereto,

[ ] was filed on _____ as

Application Serial No _____

and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (patented, pending, abandoned)
922,155	October 23, 1986	Pending

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of first joint inventor Mark L. Collins

Inventor's signature Mark L Collins

Date Dec 17, '87

Residence 435 Malden Street, Holden, Massachusetts 01520

Citizenship United States

Post Office Address 435 Malden Street, Holden, Massachusetts 01520

Full name of second joint inventor Donald N. Halbert

Inventor's signature Donald N Halbert

Date Dec. 17, 1987

Residence 31 Janock Road, Milford, Massachusetts 01757

Citizenship United States

Post Office Address 31 Janock Road, Milford, Massachusetts 01757

Full name of third joint inventor Walter King

Inventor's signature Walter King

Date Dec 14, 1987

Residence Three Fletcher Street, Maynard, Massachusetts 01754

Citizenship United States

Post Office Address Three Fletcher Street, Maynard, Massachusetts 01754

*Dr. Jonathan M. Lawrie's signature to the above declaration is contained

*

Full name of fourth joint inventor Jonathan M. Lawrie

Inventor's signature Jonathan M. Lawrie

Date 12/17/87

Residence S. Oak Terrace, Milford, Massachusetts 01757

Citizenship United States

Post Office Address S. Oak Terrace, Milford, Massachusetts 01757

Form 28-58 (4-87)
(Joint Inventors)

Petition and Power of Attorney

To the Commissioner of Patents and Trademarks:

Your petitioners, Mark L. Collins whose

Post Office address is 435 Malden Street

and who is a resident of Holden, County of Worcester,

State of Massachusetts; Donald N. Halbert whose

Post Office address is 31 Janock Road

and who is a resident of Milford, County of Worcester,

State of Massachusetts, ~~and~~ Walter King whose

Post Office address is Three Fletcher Street

and who is a resident of Maynard, County of Middlesex,

State of Massachusetts and Jonathan M. Lawrie whose

Post Office address is S. Oak Terrace,

and who is a resident of Milford, County of Worcester,

State of Massachusetts;

citizens of the United States, pray that Letters Patent be granted to them for the improvement in

TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS

set forth in the annexed specification; and they hereby appoint Ralph C. Medhurst Registration No. 20,082; William H. Magidson Registration No. 19,902; Robert J. Wagner Registration No. 24,186; and Anthony J. Janiuk Registration No. 29,809

their attorneys; the address of each being, Amoco Corporation, Patents and Licensing Department, Mail Code 1907A, 200 East Randolph Drive, P. O. Box 87703, Chicago, Illinois 60680-0703; each of said attorneys to have full power to prosecute this application, to receive the patent, and to transact all business in the Patent and Trademark Office connected therewith, said Ralph C Medhurst, said William H Magidson, and said Robert J. Wagner each to have in addition full power of substitution, association and revocation, including the power to revoke the power of attorney of said Anthony J. Janiuk

The Patent and Trademark Office is requested to direct all mail to said Anthony J. Janiuk

and all telephone calls to said Anthony J. Janiuk

at 312- 856-7972.

FIG. Ia

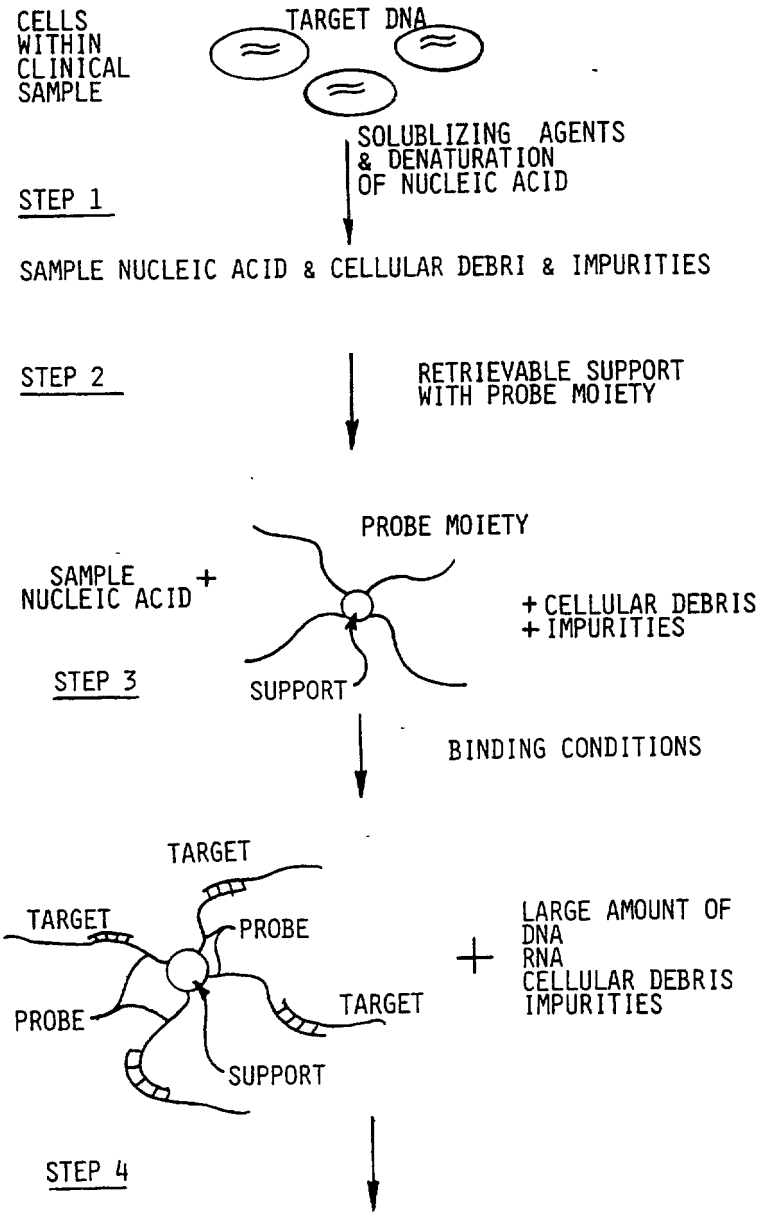


FIG. 1b

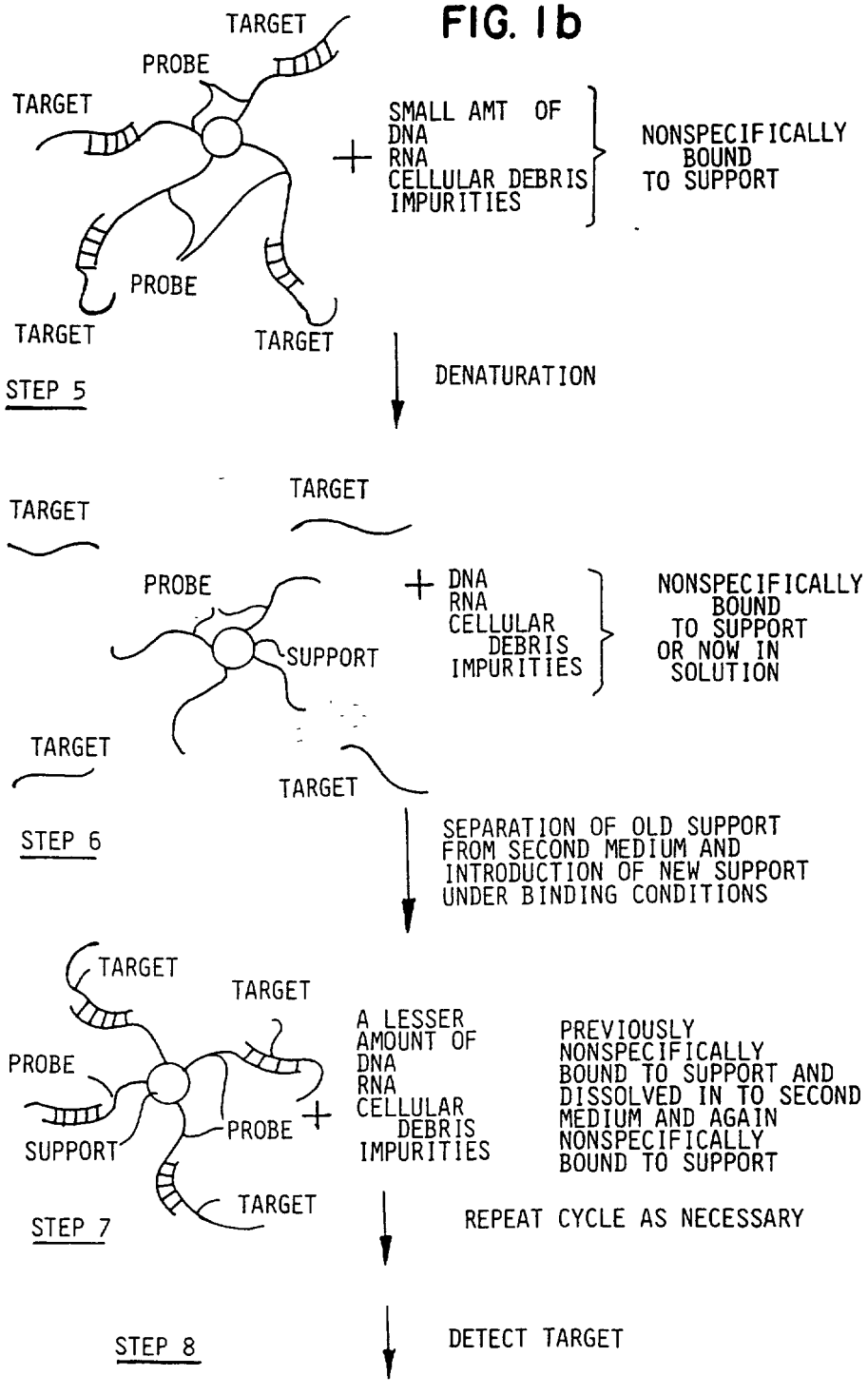


FIG. 2a

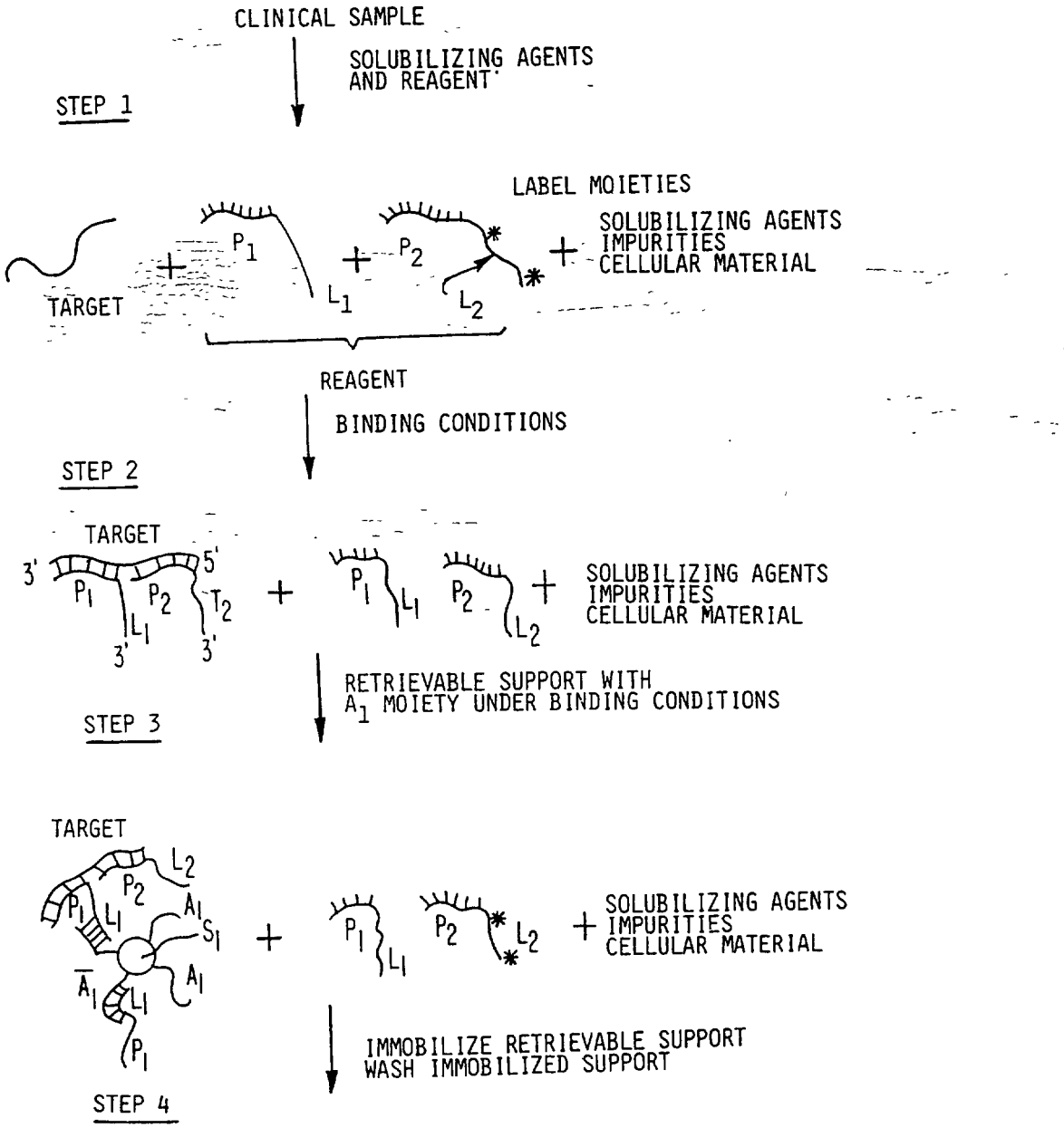


FIG. 2b

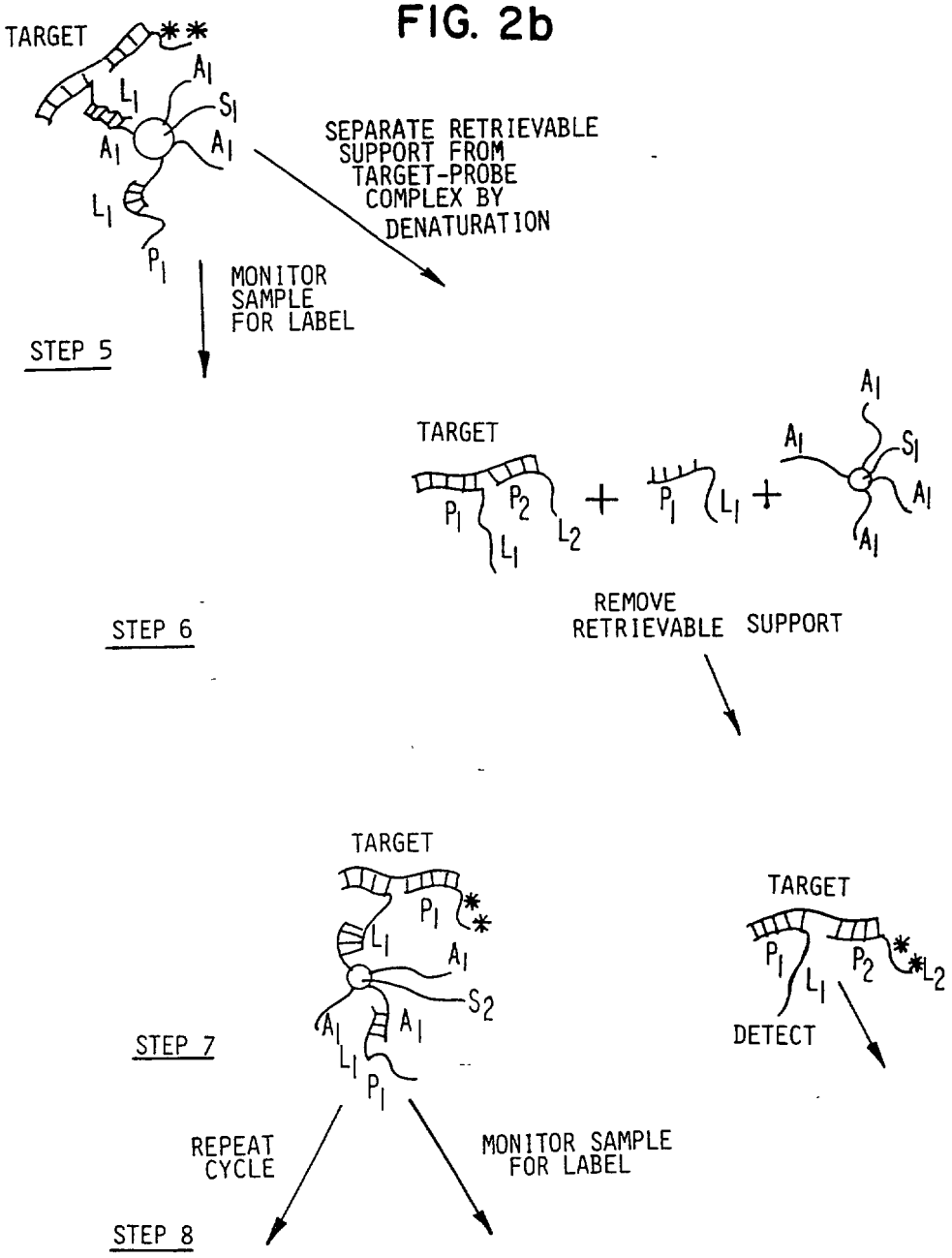


FIG. 3

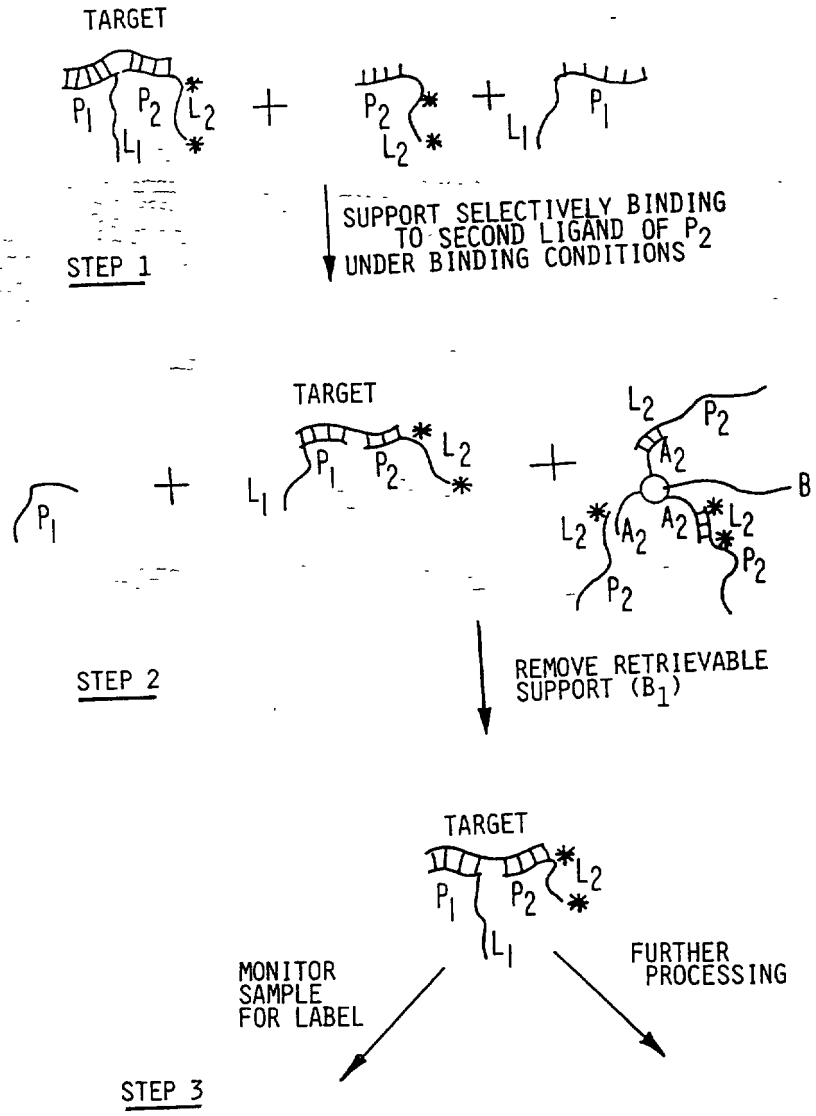


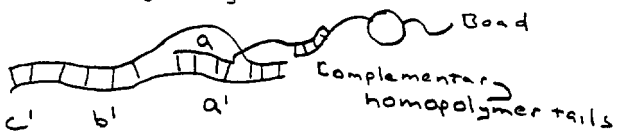
Fig 4

Print Of Drawing
As Original Filed

Target ... sample

Step 1

capture probe (recA protein coated)
capture bead
Binding conditions



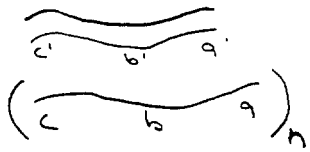
Step 2

isolate beads

target DNA (substantially free of sample impurities, debris, extraneous polynucleotides)

Step 3

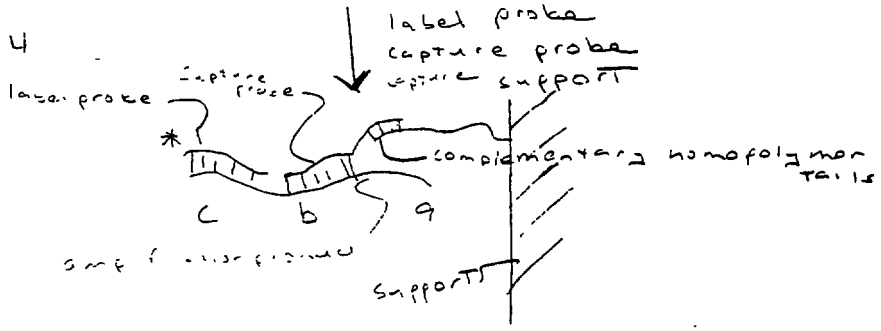
core RNA polymerase
Low salt Buffer



target DNA
RNA complementary to target DNA

Step 4

label probe
capture probe
capture support



Print Of Drawing
As Original Filed

Fig 5

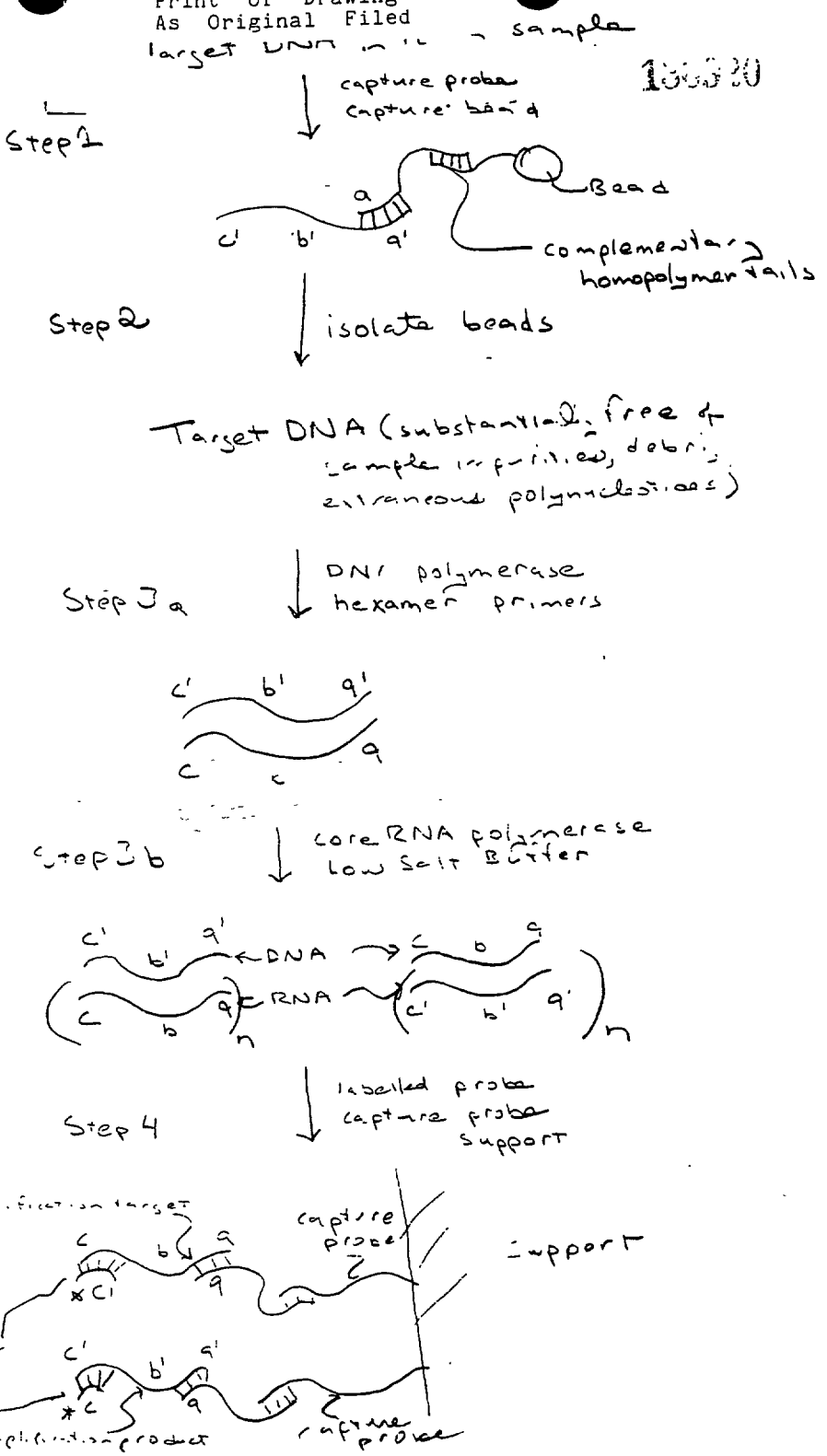


Fig 6

Print Of Drawing
As Original Filed

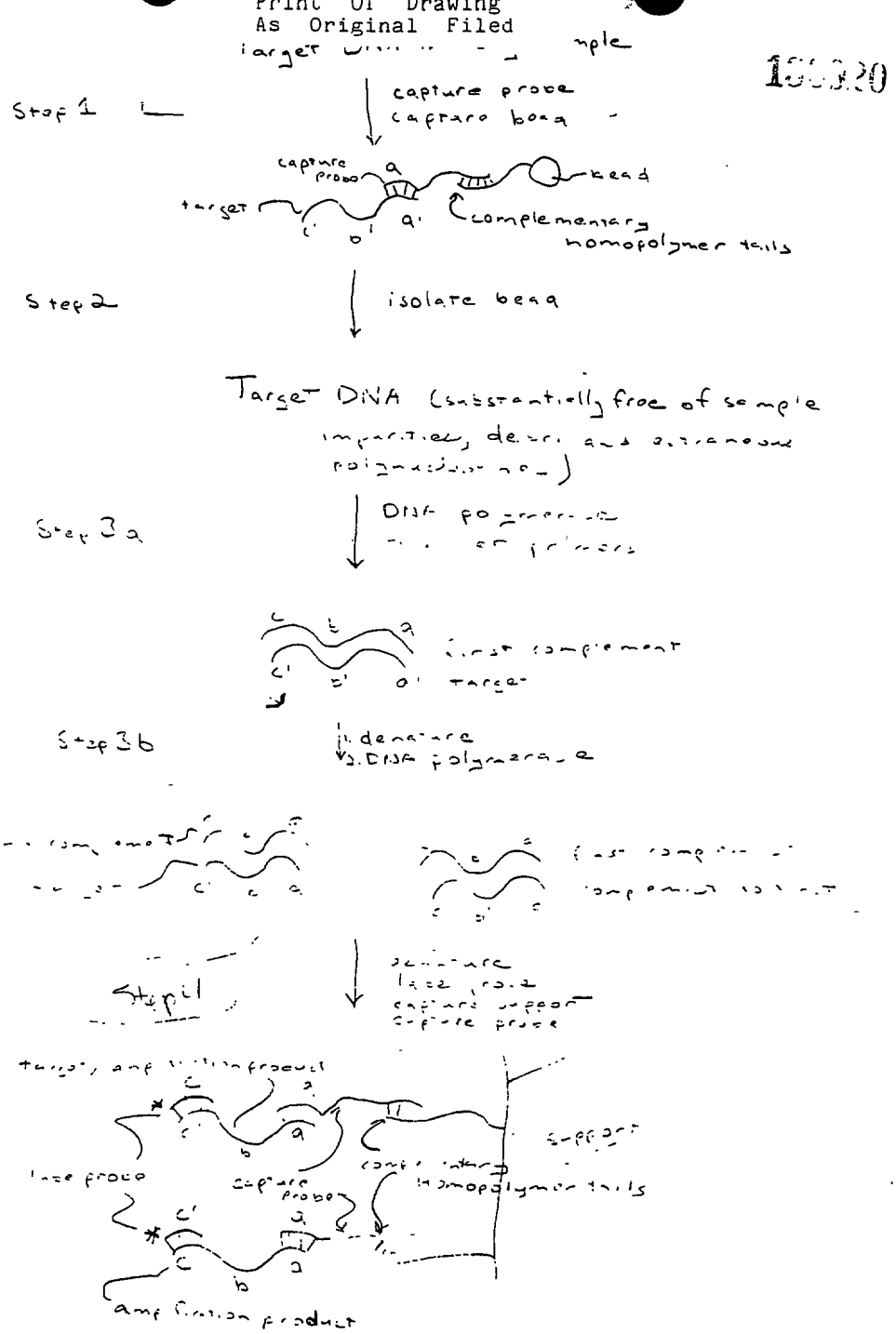
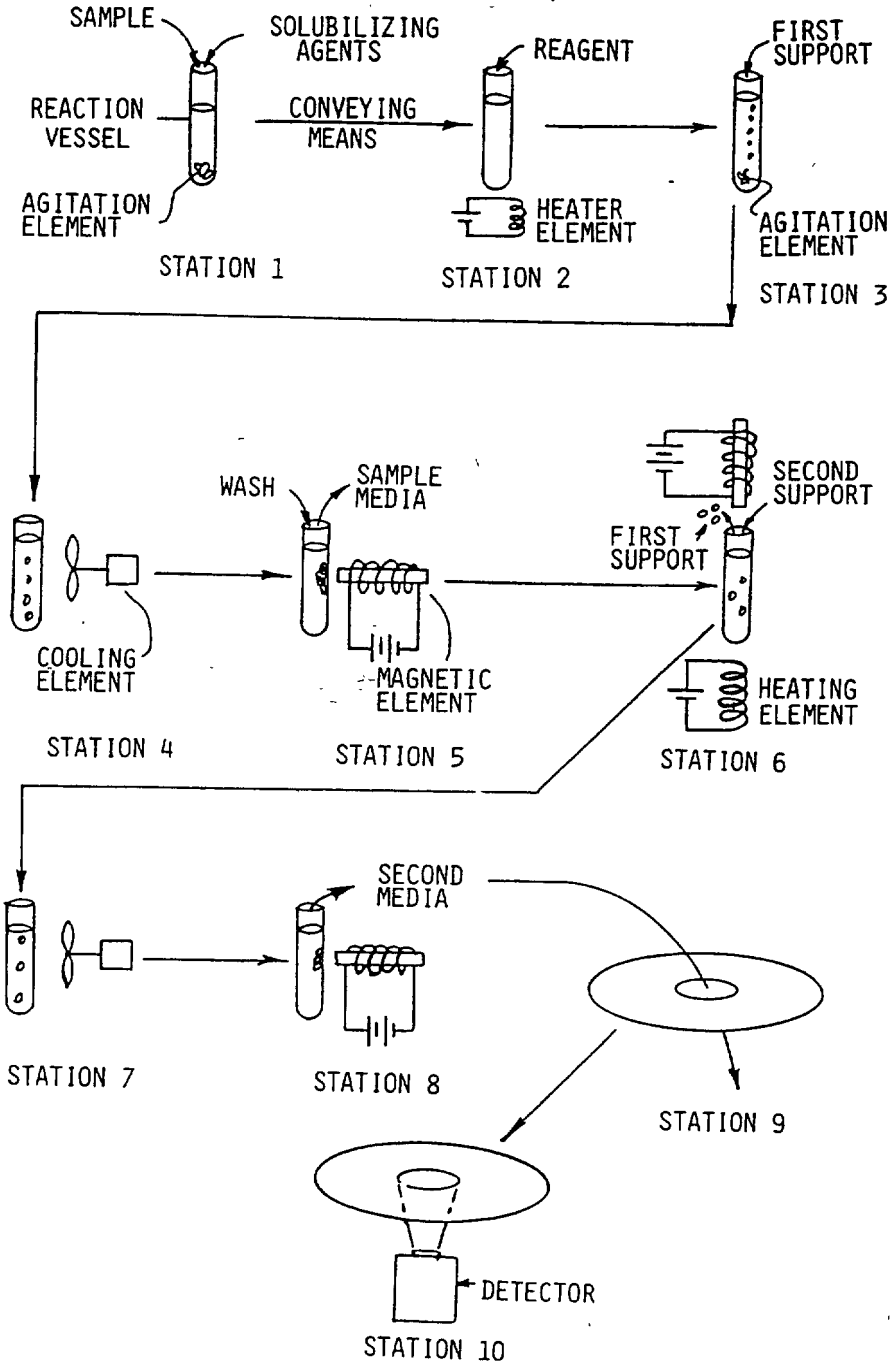


FIG. 7



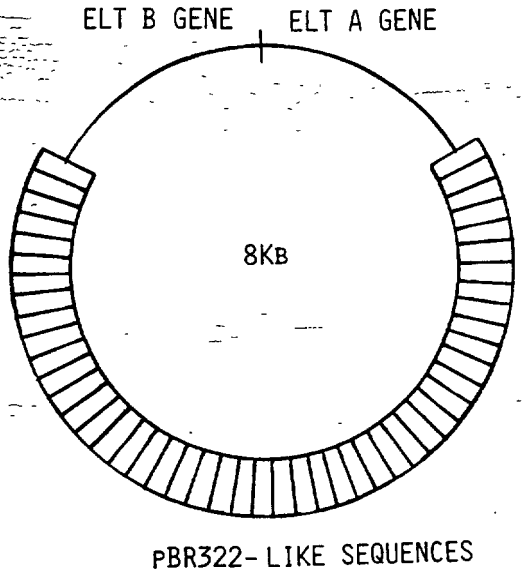


FIG. 8

U.S. Depar. -t of Commerce
Patent Office 136920

Adress Only: **Commissioner of Patents**
Washington, D.C. 20231

Case Docket No. 25,83501

December 18, 1987

The Commissioner of Patents
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application for

Inventor: Mark L. Collins; Donald N. Halbert; Walter King and Jonathan M. Lawrie

For: TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS (Collins-Halbert-King-Lawrie CIP of S.N. 922,155)

Enclosed are

[x] 10 sheets of drawing. (Informal)

[ ] A certified copy of a _____ application.

[ ] Associate power of attorney.

Claims As Filed					
	(1) For	(2) Number Filed	(3) Number Extra	(4) Rate	(5) Basic Fee $340.00
	Total Claims	24 -20-	4	$12.00	48.00
	Independent Claims	4 -3-	1	$34.00	34.00
				Total Filing Fee ▶	$422.00

[ ] Please charge to Deposit Account No. _____ in the amount of $ _____.
A duplicate copy of this sheet is enclosed.

[x] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Account No. 01-0528. A duplicate copy of this sheet is enclosed.

[x] A check in the amount of $ 422.00 to cover the filing fee is enclosed.

ANTHONY J. JANIUK
Attorney of Record
Registration No. 29,809
Attorney for Applicants

26-50 (2-86)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

07/136,920 12/21/87 COLLINS M 25,83501

CHAMBERS, S

AMOCO CORPORATION
MAIL CODE 1907 A
200 EAST RANDOLPH DR.
P. O. BOX 87703
CHICAGO, IL 60680-0703

187

~~06/27/90~~
REMAILED
JUL 20 1990
GROUP 180

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-24 are pending in the application.
   Of the above, claims 24 15 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-23 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 6-88)

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 180 Art Unit 187.

Applicants are encouraged to file an information disclosure statement including (1) a form PTO-1449, "Information Disclosure Citation" listing patents, publications, seminars, and other information material to the instant application; (2) a concise explanation of the relevance of each listed item; and (3) a copy of each listed item as a means of complying with the duty of disclosure set forth in 37 CFR 1.56. See 37 CFR 1.97 through 1.99 and MPEP 609.

The application is objected to because of alterations which have not been initialed and/or dated as is required by 37 CFR 1.52(c) and 1.56.

A properly executed affidavit or declaration signed by all of the inventors identifying the alterations and stating when the unsigned and/or undated alterations were made is required.

If the alterations were made *before* the signing of the oath or declaration, a new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by its Serial Number, filing date and the title is also required.

If the alterations were made *after* the signing of the oath or declarations, a full explanation and cancellation of such alterations is required.

The alterations are found on page 28 where line 33 has a "3" with an ink line drawn through it and a superscript "1" added.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-23, drawn to a method of nucleic acid amplification, classified in Class 435, subclass 6 and 91.

II. Claim 24, drawn to an apparatus and measuring device, classified in Class 435, subclass 291 & 293.

The inventions are distinct, each from the other because of the following reasons: Inventions I and II are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP 806.05(e)). In this case the process as claimed can be practiced by hand as pointed out in the disclosure.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and different classification, as well as the fact that the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

During a telephone conversation with Anthony J. Janiuk on January 4, 1990, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-23. Affirmation of this election must be made by applicant in responding to this Office action. Claim 24 is withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Claims 1-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and others recite "support capable of specifically associating with the target under binding conditions" which is vague and indefinite functional language describing a chemical moiety by what it does rather than by what it is structurally; therefore it is impossible to know what is and

what is not claimed. Claim 6 recites "probe" which is vague and indefinite: do applicants intend a specific nucleic acid sequence which will probe through hybridization or is something else intended? Claim 6 also is phrased in functional language. Claim 10 recites "transcriptase" which is vague and indefinite: was "reverse transcriptase" contemplated? Claim 11 and others recite "non-specific oligonucleotide primer" which is vague and indefinite. Claim 13 and others recite "substantially separating" which is vague and indefinite. Claim 21 recites "capable of binding to a retrievable support" which is vague and indefinite functional language. The claims also recite "retrievable support" but it is not clear what support would not be retrievable: thus it is confusing. It also recites "reagents adapted to be applied to said removal product" which is vague and indefinite. Claim 22 (and claim 23 since it depends on claim 22) refer to the "method of claim 21", but claim 21 is a kit claim corresponding to various compositions of matter: it is not a method claim. This makes claims 22 and 23 confusing. Claim 23 recites "capable of interacting with a magnetic field" which is vague and indefinite: in light of the known ability of any carbon, nitrogen, or hydrogen containing compound to interact with a magnetic field (e.g. NMR) it is not clear what applicants are describing.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-23 are rejected under 35 U.S.C. 103 as being unpatentable over any one of Mullis, Mullis et al., or Mullis et al. (ref. R) when taken with

any one of Moss et al., Wood et al., Noyes et al., Shih et al., Stabinsky or Engelhardt et al. and taken further in view of Ranki et al. or Josephson or Schroder if necessary.

The primary references all teach DNA amplification and point out the great value of this method for improved sensitivity as well as improved ability to isolate specific nucleotide sequences. The primary references do not specifically teach nucleic acid affinity chromatography prior to the amplification reaction. The secondary references all teach the well known method of affinity chromatography, both with nucleic acid attached to a support (direct hybridization) as well as through ligands attached to one strand of the nucleic acid (e.g. biotin-avidin). The secondary references teach the value of affinity chromatography in its ability to isolate specific nucleotide sequences and remove unwanted sequences which would interfere with later usefulness of the sequences. The secondary references also teach the greater efficiency of hybridization and improved sensitivity of an affinity purified sample compared to a non-purified sample (e.g. Moss et al. figure 3) although this fact would be well known to one of ordinary skill in the art. It would be obvious for one of ordinary skill in the art to combine the teachings of the primary references which show improved sensitivity and improved ability to purify a sequence with the secondary references which teach a method providing improved ability to purify a sequence and improved sensitivity since the methods are all directed to the same result and one of ordinary skill would expect an improvement in results.

In regard to claims directed to association with a "probe": it is not clear what applicants mean by this language (see supra); however, it appears to be the well known method of sandwich hybridization (see Ranki et al., this reference has not been provided, it was provided in previous Office Actions on the parent case and it is assumed that applicants are familiar with it) which also claims increased sensitivity and greater ability to isolate specific sequences. In regards to "non-specific oligonucleotide primer": it is not clear what applicants mean by this language (see supra); however, it appears that applicants are simply referring to the well known method of random primer polymerization which is used to label probes. This method is well known not only as an efficient method of making a second copy (into which labeled

nucleotides can be added) but is also more efficient than using a single primer. One of ordinary skill in the art would have known this technique and would have been motivated to use it since it makes a second strand thereby doubling the number of copies to be amplified. In regards to the use of a "bead capable of interacting with a magnetic field": it is not clear what applicants mean by this language (see supra); however, it appears to be the well known method of Josephson and Schroder for magnetic separations (these references have not been provided, they were provided in previous Office Actions on the parent case and it is assumed that applicants are familiar with them). In regards to the kit claims: it would have been obvious to one of ordinary skill in the art to package all of the components in a kit for the convenience of practitioners of the method.

To clarify this rejection, it is examiner's position that applicants simply combined the well known method of nucleic acid amplification with the equally well known method of affinity chromatography to produce a result which would have been expected and with sufficient motivation to make the combination. Thus applicants invention would have been prima facie obvious at the time of the invention to one of ordinary skill in the art.

No claim is allowed.

An inquiry concerning this communication should be directed to Scott A Chambers, Ph.D. at telephone number 703-557-0117.

AMELIA BURGESS YARBROUGH
PRIMARY EXAMINER
ART UNIT 187

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED		07/136,920	187	
		APPLICANT(S) Collen's		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
V	A	4,672,040	June 9/87	Josephson	436	526	June 28/85
V	B	4,471,058	Sep 11/84	Smith et al	436	518	
V	C	4,486,539	Dec 4/84	Ranki et al	436	504	
V	D	4,687,748	Aug 18/87	Schröder	436	526	Mar 23/83
	E	4,751,177	June 14/88	Stalinsky	435	6	June 13/85
	F	4,683,195	July 28/87	Mullis et al	435	6	March 28/85
	G	4,683,202	July 28/87	Mullis et al	435	91	March 28/85
	H						
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FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L	0097373	04/01/84	EP	Engelhardt	435	6		
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R Mullis et al. Cold Spring Harbor Symposia on Quantitative Biology 55 (1986) Cold Spring Harbor Press, Cold Spring Harbor N.Y. p 263-273

T Moss et al. Journal of Biological Chem. 256: 12655-58 (1981)

U Shih et al Biochemistry 13 (16): 3411-18 (1974)

EXAMINER	DATE
[signature]	6/21/90

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER	
NOTICE OF REFERENCES CITED	07/136,920	187		
	APPLICANT(S) Collins et al			

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
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	I						
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FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R Noyes et al.; Cell 5:301-11 (1975)

S Wood et al.; Journal of Biological Chemistry 252:457-63 (1977)

T

U

EXAMINER	DATE
[signature]	6/21/90

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

J.E

J.E

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address : COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

07/[illegible],967 01/22/91 COLLINS M 25.83503

CHAMBERS,S

AMOCO CORPORATION
M.C. 1007A
200 EAST RANDOLPH DRIVE
P. O. BOX 87703
CHICAGO, IL 60680-0703

1807 2

03/12/91

☒ This application has been examined ☒ Responsive to communication filed on 1/22/91 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-24 are pending in the application.
   Of the above, claims 24 is/~~are~~ withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-23 are rejected.
5. ☐ Claims _____ are objected to.
6. ☒ Claims 24 is/~~are~~ subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Serial Number 07/644,967
Art Unit 1807

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 180 Art Unit 1807.

Examiner notes that in E.I. du Pont de Nemours & Co. v. Cetus Corp., 19 USPQ2d 1174 at 1185 (N.D.Ca. 1991), the court indicated that grant proposals to the NIH and NSF were prior art due to the requirements of the Freedom of Information Act (see 45 C.F.R. §5 1 et seq. and §612 et seq.) This may be of some interest to applicants in satisfying 37 C.F.R. 1.56.

Applicants are requested to look over the specification and correct any minor errors.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-23, drawn to a method of nucleic acid amplification, classified in Class 435, subclass 6 and 91.

II. Claim 24, drawn to an apparatus and measuring device, classified in Class 435, subclass 291 & 293.

The inventions are distinct, each from the other because of the following reasons: Inventions I and II are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP 806.05(e)) In this case the process as claimed can be practiced by hand as pointed out in the disclosure.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and different classification, as well as the fact that the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

During a telephone conversation with Anthony J. Januik on January 4, 1990, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-23. Affirmation of this election must be made by applicant in responding to this Office action. Claim 24 is withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicants have indicated that the instant application is a continuation of 07/136,920

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(h).

Claims 1-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and others recite "support capable of specifically associating with the target under binding conditions" which is vague and indefinite functional language describing a chemical moiety by what it does rather than by what it is structurally; therefore it is impossible to know what is and what is not claimed. Claim 6 recites "probe" which is vague and indefinite: do applicants intend a specific nucleic acid sequence which will probe through hybridization or is something else intended? Claim 6 also is phrased in functional language. Claim 10 recites "transcriptase" which is vague and indefinite: was "reverse transcriptase" contemplated? Claim 11 and others recite "non-specific oligonucleotide primer" which is vague and indefinite. Claim 13 and others recite "substantially separating" which is vague and indefinite. Claim 21 recites "capable of binding to a retrievable support" which is vague and indefinite functional language. The claims also recite "retrievable support" but it is not clear what support would not be retrievable: thus it is confusing. It also recites "reagents adapted to be applied to said removal product" which is vague and indefinite. Claim 22 (and claim 23 since it depends on claim 22) refer to the "method of claim

21", but claim 21 is a kit claim corresponding to various compositions of matter: it is not a method claim. This makes claims 22 and 23 confusing. Claim 23 recites "capable of interacting with a magnetic field" which is vague and indefinite in light of the known ability of any carbon, nitrogen, or hydrogen containing compound to interact with a magnetic field (e.g. NMR) it is not clear what applicants are describing.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-23 are rejected under 35 U.S.C. 103 as being unpatentable over any one of Mullis, Mullis et al., or Mullis et al. (ref. R) when taken with any one of Moss et al., Wood et al., Noyes et al., Shih et al., Stabinsky or Engelhardt et al. and taken further in view of Ranki et al. or Josephson or Schroder if necessary

The primary references all teach DNA amplification and point out the great value of this method for improved sensitivity as well as improved ability to isolate specific nucleotide sequences. The primary references do not specifically teach nucleic acid affinity chromatography prior to the amplification reaction. The secondary references all teach the well known method of affinity chromatography, both with nucleic acid attached to a support (direct hybridization) as well as through ligands attached to one strand of the nucleic acid (e.g. biotin-avidin). The secondary references teach the value of affinity chromatography in its ability to isolate specific

nucleotide sequences and remove unwanted sequences which would interfere with later usefulness of the sequences. The secondary references also teach the greater efficiency of hybridization and improved sensitivity of an affinity purified sample compared to a non-purified sample (e.g. Moss et al. figure 3) although this fact would be well known to one of ordinary skill in the art. It would be obvious for one of ordinary skill in the art to combine the teachings of the primary references which show improved sensitivity and improved ability to purify a sequence with the secondary references which teach a method providing improved ability to purify a sequence and improved sensitivity since the methods are all directed to the same result and one of ordinary skill would expect an improvement in results.

In regard to claims directed to association with a "probe": it is not clear what applicants mean by this language (see supra); however, it appears to be the well known method of sandwich hybridization (see Ranki et al., this reference has not been provided, it was provided in previous Office Actions on the parent case and it is assumed that applicants are familiar with it) which also claims increased sensitivity and greater ability to isolate specific sequences. In regards to "non-specific oligonucleotide primer": it is not clear what applicants mean by this language (see supra); however, it appears that applicants are simply referring to the well known method of random primer polymerization which is used to label probes. This method is well known not only as an efficient method of making a second copy (into which labeled nucleotides can be added) but is also more efficient than using a single primer. One of ordinary skill in the art would have known this technique and would have been motivated to use it since it makes a second strand thereby doubling the number of copies to be amplified. In regards to the use of a "bead capable of interacting with a magnetic field": it is not clear what applicants mean by this language (see supra); however, it appears to be the well known method of Josephson and Schroder for magnetic separations (these references have not been provided, they were provided in previous Office Actions on the parent case and it is assumed that applicants are familiar with them). In regards to the kit claims: it would have been obvious to one of ordinary skill in the art to package all of the components in a kit for the convenience of practitioners of the method.

To clarify this rejection, it is examiner's position that applicants simply combined the well known method of nucleic acid amplification with the equally well known method of affinity chromatography to produce a result which would have been expected and with sufficient motivation to make the combination. Thus applicants invention would have been prima facie obvious at the time of the invention to one of ordinary skill in the art.

No claim is allowed.

This is a continuation of applicant's earlier application S.N. 07/136,920. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Examiner has not provided copies of any of the references cited in this Office Action because they were provided in earlier Office Actions on the parent case.

An inquiry concerning this communication should be directed to Scott A. Chambers, Ph.D at telephone number 703-308-3885.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

Scott A. Chambers
Patent Examiner
Art Unit 1807

MARGARET MOSKOWITZ
SUPERVISORY PATENT EXAMINER
GROUP 180

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED		07/644,967	1807	2
		APPLICANT(S) Collins et al.		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
V	A	4,672,040	June 9/87	Josephson	436	526	June 28/85
V	B	4,471,058	Sep 11/84	Smith et al.	436	518	
V	C	4,486,539	Dec 4/84	Ranki et al	436	504	
V	D	4,687,748	Aug 18/87	Schröder	436	526	Mar 23/83
V	E	4,751,177	June 14/88	Stalinski	435	6	June 13/85
V	F	4,683,195	July 28/87	Mullis et al	435	6	Mar 28/85
V	G	4,683,202	July 28/87	Mullis	435	91	Mar 28/85
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	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
V	L	0097373	04/01/84	EP	Englehardt	435	6		
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

V	R	Mullis et al. Cold Spring Harbor Symposia on Quantitative Biology 55 (1986) Cold Spring Harbor Press; Cold Sp. Harbor NY p 263-73
V	S	Moss et al. Journal of Biological Chem 256:12655-58 (1981)
V	T	Shih et al Biochemistry 13(16):3411-18 (1974)
V	U	Noyes et al; Cell 5 301-11 (1975)

EXAMINER	DATE
[signature]	3/11/92

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP–APART AND DISCARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED	07/644,967	1807	2
	APPLICANT(S) Collins et al.		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
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FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
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	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

✓	R	Wood et al.; Journal Biol Chem 252:457-63 (1977)
	S	
	T	
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EXAMINER	DATE
Scott Chunn	3/11/92

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

20210" 9066E560

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO
[illegible]	[illegible]	[illegible]	[illegible]

AMOCO CORPORATION
PATENTS AND LICENSING DEPT., M.C. 1907A
200 EAST RANDOLPH DRIVE
P. O. BOX 87703
CHICAGO, IL 60680-0703

EXAMINER	
CHAMBERS, S	
ART UNIT	**PAPER NUMBER**
1807	3

DATE MAILED: 11/05/92

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on Sept 14/92 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~_____ days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-24 are pending in the application.
   Of the above, claims 24 ~~24~~ 15 withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-23 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).
10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Serial Number 07/944,505
Art Unit 1807

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group 180 Art Unit 1807.

Examiner notes that in E.I. du Pont de Nemours & Co. v. Cetus Corp., 19 USPQ2d 1174 at 1185 (N.D.Ca. 1991), the court indicated that grant proposals to the NIH and NSF were prior art due to the requirements of the Freedom of Information act (see 45 C.F.R. 55.1 et seq. and 561 et seq.). This may be of some interest to applicants in satisfying 37 C.F.R. 1.56.

Applicants are requested to look over the specification and correct any minor errors.

Restriction to one of the following inventions is required under 35 U.S.C. 121.

I. Claims 1-23, drawn to a method of nucleic acid amplification, classified in Class 435 subclass 6 and 91.

II. Claim 24, drawn to an apparatus and measuring device, classified in Class 435 subclass 291 & 293.

The inventions are distinct, each from the other because of the following reasons. Inventions I and II are related as process and apparatus for its practice. The inventions are distinct if it can be shown that either: (1) the process as claimed can be practiced by another materially different apparatus or by hand, or (2) the apparatus as claimed can be used to practice another and materially different process. (MPEP 806.05(e)). In this case the process as claimed can be practiced by hand as pointed out in the disclosure.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and different classification, as well as the fact that an search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

During a telephone conversation with Norval E. Galloway on November 4, 1996, a provisional election was made with traverse to prosecute the invention of Group I, claims 1-23. Affirmation of this election must be made by applicant in responding to this Office action. Claim 24 is withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicants have indicated that the instant application is a continuation of 07/644,067 which is a continuation of 07/136,920. In both parents, Group I was elected.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and others recite "support capable of specifically associating with the target under binding conditions" which is vague and indefinite functional language describing a chemical moiety by what it does rather than by what it is structurally; therefore it is impossible to know what is and what is not claimed. Claim 6 recites "probe" which is vague and indefinite. Do applicants intend a specific nucleic acid sequence which will probe through hybridization or is something else intended? Claim 6 also is phrased in functional language. Claim 10 recites "transcriptase" which is vague and indefinite. Was "reverse transcriptase" contemplated? Claim 11 and others recite "non-specific oligonucleotide primer" which is vague and indefinite. Claim 19 and others recite "substantially separating" which is vague and indefinite. Claim 21 recites "capable of binding to a retrievable support" which is vague and indefinite functional language. The claims also recite "retrievable support" but it is not clear what support would not be retrievable, thus it is confusing. It also recites "reagents adapted to be applied to said removal product" which is vague and indefinite. Claim 22

[illegible]

[illegible] claim 31 since it depends on claim 21 refer to the method of claim 21 but claim 21 is a kit claim corresponding to various compositions of matter. It is not a method claim. This makes claims 22 and 23 confusing. Claim 23 defines "capable of interacting with a magnetic field" which is vague and indefinite in light of the known ability of any carbon, nitrogen, or hydrogen containing compound to interact with a magnetic field (e.g. NMR). It is not clear what is applicable or patentable.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action.

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention, were owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-23 are rejected under 35 U.S.C. 103 as being unpatentable over Mullis when taken with any one of Moss et al., Stabinsky or Engelhardt et al. and taken further in view of Rahn et al. or Josephson or Schroder if necessary.

The primary reference teaches DNA amplification and point out the great value of this method for improved sensitivity as well as improved ability to isolate specific nucleotide sequence. The primary references do not specifically teach nucleic acid affinity chromatography prior to the amplification reaction. The secondary references all teach the well known method of affinity chromatography both with nucleic acid attached to a support or matrix for separation as well as through ligands attached to the ends of the nucleic acid (e.g. biotin-avidin). The secondary references teach the value of affinity chromatography in its ability to isolate specific

nucleotide sequences and remove unwanted sequences which would interfere with later usefulness of the sequences. The secondary references also teach the greater efficiency of hybridization and improved sensitivity of an affinity purified sample compared to a non-purified sample (e.g. Moss et al. figure 2) although this fact would be well known to one of ordinary skill in the art. It would be obvious for one of ordinary skill in the art to combine the teachings of the primary references which show improved sensitivity [illegible] to purify a sequence with the secondary references which teach a method providing improved ability to purify a sequence and improved sensitivity since the methods are all directed to the same result and one of ordinary skill would expect an improvement in results.

In regard to claims directed to association with a "probe" it is not clear what applicants mean by this language (see supra), however, it appears to be the well known method of sandwich hybridization (see Sanki et al., this reference has not been provided it was provided in previous Office Actions in the parent case and it is assumed that applicants are familiar with it) which also claims increased sensitivity and greater ability to isolate specific [illegible] it is not clear what applicants mean by this language (see supra) however it appears that applicants are simply referring to the well known method of random primer polymerization which is used to label probes. This method is well known not only as an efficient method of making a second copy onto which labeled nucleotides can be added but is also more efficient than using a single primer. One of ordinary skill in the art would have known this technique and would have been motivated to use it since it makes a second strand thereby doubling the number of copies to be amplified. In regards to the use of a "head capable of interacting with a magnetic field" it is not clear what applicants mean by this language (see supra), however, it appears to be [illegible] and that are not magnetic separations [illegible] they were provided in previous Office Actions on the parent case and it is assumed that applicants are familiar with them. In regards to the kit claims it would have been obvious to one of ordinary skill in the art to package all of the components in a kit for the convenience of practitioners of the method.

To clarify this rejection, it is Examiner's position that applicants simply combined the well known methods of size and affinity chromatography to produce a result that would have been expected and with sufficient expectation to make the combination. Thus applicant's invention would have been prima facie obvious at the time of the invention to one of ordinary skill in the art.

Examiner notes that Wood et al., Noyes et al., and Shih et al., which were supplied in previous Office Actions, are merely cumulative to the teachings of Moss et al., Stabinsky and Engelhardt et al. Mullis et al. and Mullis et al. (ref. R) are merely cumulative to Mullis.

No claim is allowed.

This is a continuation of applicant's earlier application SN [illegible]. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art [illegible] the next Office action if they had been entered in the earlier application. Accordingly, THIS ACTION IS MADE FINAL even though it is the first action in this case. See 37 CFR 1.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon the filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RECPONCE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE [illegible] WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY

Serial Number: 09/[illegible],505
Art Unit: 1807

PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION

Applicant has not provided copies of any of the references cited in this Office Action because they were provided in earlier Office Actions in the present case.

An inquiry concerning this communication should be directed to Scott A. Chambers, Ph.D. at telephone number 703-308-3885.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center, located in Crystal Mall 1. The filing of such papers must conform with the notice published in the Official Gazette [illegible] (November 15, [illegible]). The GM Fax Center number is (703) 308-4227.

Scott A. Chambers
Patent Examiner
Art Unit 1807

MARGARET MOSKOWITZ
SUPERVISORY PATENT EXAMINER
GROUP 180

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP-APART AND DISCARD CARBON

FORM PTO-892 (REV 3-78)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO. 7/944,515	GROUP ART UNIT 1807	ATTACHMENT TO PAPER NUMBER	
NOTICE OF REFERENCES CITED		APPLICANT(S) Collins			

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
V	A	4,672,040	June 9/87	Josephson	436	526	June 28/85
V	B	4,471,058	Sep 11/84	Smith et al	436	518	
V	C	4,486,539	Dec 4/84	Ronki et al	436	504	
V	D	4,687,748	Aug 18/87	Schröder	436	526	Mar 23/83
V	E	4,751,177	June 14/88	Statinsky	435	6	June 3/85
V	F	4,683,195	July 28/87	Mullis et al	435	6	March 28/85
V	G	4,683,202	July 28/87	Mullis	435	91	March 28/85
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
V	L	0097373	04/01/84	EP	Engelhardt	435	6		
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

V	R	Mullis et al Cold Spring Harbor Symposia on Quant. Biol. 55 (1986); Cold Spring Harbor Press, CSH N.Y. pp 263-73
V	S*	Moss et al Journal of Biol Chem 256: 12655-58 (1981)
V	S	Shih et al Biochemistry 13(16): 3411-18 (1974)
V	T	Noyes et al., Cell 5 301-11 (1975)
V	U	Wood et al, Journal of Biol Chem 252: 457-63 1977

EXAMINER	DATE
[signature]	11/4/92

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

PTO FORM 948
(Rev 5-91)

U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

ATTACHMENT TO PAPER NUMBER

APPLICATION NUMBER 944505

GROUP

NOTICE OF DRAFTSMAN'S PATENT DRAWING REVIEW

The PTO Draftsmen review all originally filed drawings regardless of whether they were designated as informal or formal.

The drawings filed 9/14/92

A ☐ are approved

B ☒ are objected to under 37 CFR 1.84 or 1.152 for the reason(s) checked below. The examiner requires submission of new corrected drawings at the appropriate time. Corrected drawings must be submitted according to the instructions listed on the back of this Notice.

1. Paper and Ink. 37 CFR 1.84(a)
   - ☐ Poor Quality Paper. Must be White.
   - ☐ Transparent Paper Not Allowed.
   - Fig(s) _____

2. Size of Sheet and Margins. 37 CFR 1.84(f)

Acceptable Paper Sizes and Margins

Margin	Paper Size: 8½ by 14 inches	11 inches	DIN Size A4: 21 by 29.7 cm
Top	2 inches	1 inch	2.5 cm
Left	1/4 inch	1/4 inch	2.5 cm.
Right	1/4 inch	1/4 inch	1.5 cm.
Bottom	1/4 inch	1/4 inch	1.0 cm

   - ☐ Proper Size Paper Not Used. All Sheets Must be Same Size
   - ☒ Proper Margins Not Used. Sheet(s) 6-8
     - ☒ Top ☐ Right
     - ☐ Left ☐ Bottom

3. Character of Lines. 37 CFR 1.84(c)
   - ☒ Lines Pale, Rough and Blurred, or Jagged. Fig(s) 4-6
   - ☐ Solid Black Shading Not Allowed. Fig(s) _____

4. ☐ Photographs Not Approved

☐ Comments

5. Hatching and Shading. 37 CFR 1.84(d)
   - ☐ Shading Not Required
   - ☐ Cross-Hatching Not Allowed
   - ☐ Double Line Hatching Not Allowed. Fig(s) _____
   - ☐ Parts in Section Must be Hatched Properly. Fig(s) _____

6. Reference Characters. 37 CFR 1.84(f)
   - ☒ Reference Characters Poor or Rough and Blurred. Fig(s) 4-6
   - Minimum 1/8 inch (3.2 mm) in height
   - ☒ Reference Characters Not Enclosed in Circles. Fig(s) 4-7

7. Views. 37 CFR 1.84(g) & (j)
   - ☐ Figures Must be Numbered Separately.
   - ☐ Figures Must Not be Connected Fig(s) _____

8. Identification of Drawings. 37 CFR 1.84(l)
   - ☐ Extraneous Matter or Copy Machine Marks Not Allowed. Fig(s) _____

9. ☐ Changes Not Completed from Prior PTO-948 dated _____

Telephone inquires concerning this review should be directed to the Chief Draftsman at telephone number (703) 557-6404.

WMS — Reviewing Draftsman

9/30/92 — Date

PTO Copy

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Collins et al.	Art Unit:	1807
Serial No:	08/283,080	Examiner:	Rees, D.
Filed:	May 3, 1994		
For:	TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS	Docket No:	2583511

pre-A. / election 8/4/95 11/6/96

PRELIMINARY AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

Please amend the application as follows.

In the Specification:

Please insert the following as the first sentence of the specification following the title:

This is a ~~divisional~~ continuation of U.S. Serial No. 08/400,657 filed March 8, 1995.

Please cancel Claims ~~1-24~~ and replace them with the following new Claims 25-50:

~~25.~~ A method for amplifying a target polynucleotide contained in a sample comprising the steps of:

(a) contacting the sample with a first support which binds to the target polynucleotide;

(b) substantially separating the support and bound target polynucleotide from the sample; and

(c) amplifying the target polynucleotide.

26. The method of Claim 25 wherein the first support is retrievable.

27. The method of Claim 25 wherein the first support includes a probe which binds with the target polynucleotide.

28. The method of Claim 25 wherein the target polynucleotide is amplified with a polymerase.

29. The method of Claim 28 wherein the polymerase is a DNA polymerase, an RNA polymerase, a transcriptase or Qβ replicase.

30. The method of Claim 28 wherein the target polynucleotide is a DNA polynucleotide and the polymerase is a DNA polymerase.

31. A method for detecting a target polynucleotide contained in a sample comprising the steps of:

(a) contacting the sample with a first support which binds to the target polynucleotide;

(b) substantially separating the first support and bound target polynucleotide from the sample;

(c) amplifying the target polynucleotide; and

(d) detecting the presence of the amplified target polynucleotide.

32. The method of Claim 31 wherein the first support is retrievable.

33. The method of Claim 31 wherein the first support includes a probe which binds with the target polynucleotide.

34. The method of Claim 31 wherein the target polynucleotide is amplified with a polymerase.

11 ~~35.~~ The method of Claim ~~34~~ 10 wherein the polymerase is a DNA polymerase, an RNA polymerase, a transcriptase or Qβ replicase.

12 ~~36.~~ The method of Claim ~~35~~ 11 wherein the target polynucleotide is a DNA polynucleotide and the polymerase is a DNA polymerase.

13 ~~37.~~ The method of Claim ~~31~~ 7 wherein the amplified target polynucleotide is contacted with a label.

14 ~~38.~~ The method of Claim ~~31~~ 7 wherein the amplified target polynucleotide is contacted with a labeled probe.

15 ~~39.~~ The method of Claim ~~31~~ 7 wherein the amplified target polynucleotide is contacted with a second support which binds to the amplified target polynucleotide.

16 ~~40.~~ The method of Claim ~~39~~ 15 wherein the amplified target polynucleotide is contacted with a labeled probe.

17 ~~41.~~ The method of Claim ~~40~~ 14 wherein the target polynucleotide is amplified with a polymerase.

18 ~~42.~~ The method of Claim ~~41~~ 17 wherein the target polynucleotide is a DNA polynucleotide and the polymerase is a DNA polymerase.

~~43.~~ A method for detecting a target polynucleotide contained in a sample comprising the steps of:

(a) contacting the sample with a first support which binds to the target polynucleotide;

(b) substantially separating the first support and bound target polynucleotide from the sample;

(c) amplifying the sample with a DNA polymerase;

(d) contacting the amplified target polynucleotide with a second support which binds to the amplified target polynucleotide and a labeled probe which binds to the target polynucleotide; and

(e) detecting the presence of the amplified target polynucleotide.

44. A kit for detecting a target polynucleotide contained in a sample comprising:

(a) means for substantially separating the target polynucleotide from the sample;

(b) means for amplifying the target polynucleotide;

(c) means for binding the amplified target polynucleotide to a solid medium; and

(d) means for labeling the amplified target polynucleotide.

45. The kit of Claim 44 wherein:

(a) the means for substantially separating the target polynucleotide from the sample include a first support;

(b) the means for amplifying the target polynucleotide include a polymerase;

(c) the means for binding the amplified target polynucleotide to a solid medium include a second support which binds to the amplified target polynucleotide; and

(d) a detector probe for labeling the amplified target polynucleotide.

22 ~~46~~ 21. The kit of Claim ~~45~~ further comprising a capture probe which binds to the first support and to the target.

22 ~~47~~ 22. The kit of Claim ~~46~~ wherein the polymerase is a DNA polymerase and the detector probe is labeled.

24 ~~48~~ 23. A kit for amplifying a target polynucleotide contained in a sample comprising:

(a) means for substantially separating the target polynucleotide from the sample and

(b) means for amplifying the target polynucleotide.

25 ~~49~~. The kit of Claim ~~48~~ 24 wherein:

(a) the means for substantially separating the target polynucleotide from the sample includes a support which binds to the target polynucleotide and

(b) the means for amplifying the target polynucleotide includes a polymerase.

26 ~~50~~. The kit of Claim ~~49~~ 25 wherein:

(a) the polymerase is a DNA polymerase; and

(b) the means for substantially separating the target polynucleotide from the sample includes a probe which binds to the target polynucleotide and the support.

REMARKS

I. Status Of The Application

A. The Application Is A Divisional Of U.S. Serial No. 08/400,657.

The subject application (Serial No. 08/283,080) was filed as an original application. However, as discussed herein, the application is entitled to the benefit of consideration as a divisional application to copending application U.S. Serial No. 08/400,657 filed March 8, 1995. U.S. Serial No. 08/400,657 is itself a continuation application to U.S. Serial No. 08/257,469, filed June 8, 1994 and now abandoned. U.S. Serial No. 08/257,469 is a continuation application to U.S. Serial No. 08/124,826 filed September 21, 1993 and now abandoned. Thus, U.S. Serial No. 08/400,657 claims priority from U.S. Serial No. 08/124,826 filed September 21, 1993.

Applicants are permitted to cross-reference the subject application with and claim the benefit of the earlier priority date of Serial No. 08/400,657 and U.S. Serial No. 08/124,826 pursuant to 37 CFR §1.78. Specifically, 37 CFR §1.78(a)(1) provides that a nonprovisional application may claim an invention disclosed in one or more prior filed copending nonprovisional applications. In order for this to be proper, each prior filed copending application must name as an inventor at least one inventor named in the later filed nonprovisional application and disclose the named inventor's invention in at least one claim of the later filed nonprovisional application in the manner provided by the first paragraph of 35 USC §112. In addition, each prior application must be:

(i) Complete as set forth in §1.51(a)(1), or

(ii) Entitled to a filing date as set forth in §.53(b)(a), §1.60 or §1.62 and include the basic filing fee set forth in §1.16; or

(iii) Entitled to a filing date as set forth in §1.53(b)(1) and have paid therein the processing and retention fee set forth in §1.21(1) within the time period set forth in §1.53(d)(1).

Finally, as required by 37 CFR §.78(a)(2), a nonprovisional application claiming the benefit of one or more prior filed copending nonprovisional applications must contain or be amended to contain in the first sentence of the specification following the title a reference to each such prior application, identifying it by application number. As discussed herein, the subject application satisfies these conditions.

First, neither application claims status as a provisional application so that §1.78(a)(1) and (2) are the applicable provisions of §1.78. Next, both the subject application and Serial No. 08/400,656 name Mark Collins as an inventor. Next, the priority application (Serial No. 08,400,656) discloses Collins' invention as claimed in at least one claim of the later filed application (the subject application). This is true because Serial No. 08/400,656 and Serial No. 08/124,826 are continuations-in-part applications to U.S. Serial No. 07/136,920, which is substantively identical to the subject application and specifically incorporated by reference in Serial No. 08/400,656 (See the first sentence of the priority application of Serial No. 08/400,656 enclosed herewith as Appendix 1). Next, Serial No. 08/400,656 and Serial No. 08/124,836 were complete as set forth in §1.51(a)(1). Finally, Applicants have amended the specification to contain in the first sentence following the title a reference to Serial No. 08/477,656, identifying it by application number.

B. U.S. Serial No. 08/400,657 claims priority from U.S. Serial No. 07/136,920.

As discussed, Serial No. 08/400,657 is itself a continuation application of U.S. Serial No. 08/257,469 filed June 8, 1994. Moreover, Serial No. 08/257,469 is a continuation application of U.S. Serial No. 08/124,826 filed September 21, 1993 and now

abandoned. Serial No. 08/124,826 is a continuation application of U.S. Serial No. 946,749 filed September 17, 1992 and now abandoned. Serial No. 946,749 is a continuation application of U.S. Serial No. 07/648,468 filed January 31, 1991 and now abandoned. Serial No. 07/648,468 is a continuation-in-part application of U.S. Serial No. **07/136,920** filed December 21, 1987 and now abandoned. Serial No. **07/136,920** is a continuation-in-part application of U.S. Serial No. 06/922,155 filed October 23, 1986 and now abandoned. The disclosures of both of Serial No. **07/136,920** and 06/922,155 are incorporated into the subject application by reference.

C. The Application Is Substantively Identical To U.S. Serial No. 07/944,505[1].

The subject application (Serial No. 08/283,080) is also substantively identical to U.S. Serial No. 07/944,505, filed September 14, 1992 and now abandoned. Serial No. 07/944,505 is a continuation application to U.S. Serial No. 07/644,967 filed January 22, 1991 and now abandoned. Serial No. 07/644,967 is a continuation application to U.S. Serial No. **07/136,920** filed December 21, 1987 and now abandoned. As mentioned, Serial No. **07/136,920** is a continuation-in-part application to U.S. Serial No. 06/922,155 filed October 23, 1986 and now abandoned. U.S. Serial No. **07/136,920** and No. 06/922,155 are the same applications which begin the chain of applications described earlier as underlying U.S. Serial No. 08/400,657, and incorporated by reference therein.

D. The Application Is Subject To A Restriction Requirement.

The subject application has not yet been examined but is subject to a restriction requirement mailed September 5, 1995. The subject application comprises 24 claims. Claims 1-20 and 22-23 are nominally to methods for amplifying target polynucleotides. Claim 21 is to a kit for capturing and amplifying a target polynucleotide. Claim 24 is to an instrument for performing assays for target nucleotides. The Examiner has found two groups of inventions. Group I comprises Claims 1-23 drawn to a method of amplification

[1]As a point of clarification, Applicants had intended to file the subject application as a continuation application to U.S. Serial No. 07/944,505. However, Applicants inadvertently lost copendency between the two applications thereby necessitating this alternative action.

of a target polynucleotide. Group II comprises Claim 24 is drawn to an instrument for assaying for target polynucleotides. In light of the newly amended claims, Applicant elects the claims to methods and has cancelled Claim 24 from the application. Similarly, U.S. Serial No. 07/944,505 was examined and subjected to a restriction requirement. Claims 1-23 were elected for prosecution. Claim 24 was withdrawn from consideration. Claims 1-23 were examined and rejected in an Office Action mailed November 5, 1992. As will be discussed more fully herein, this Preliminary Amendment is submitted to address the Office Action mailed November 5, 1992.

II. The Official Action Mailed November 5, 1992 For U.S. Serial No. 07/944,505

A. The status of U.S. Serial No. 07/944,505

U.S. Serial No. 07/944,505 included the same 24 claims filed with the subject application. The application was examined and an Official Action was mailed November 5, 1992. A copy of the action is enclosed for the Examiner's benefit as Appendix 2. Claims 1-24 were subject to a restriction requirement. Claim 24 was withdrawn from consideration. Claims 1-23 were elected and examined. All of Claims 1-23 were rejected and the rejection was made final. Applicants' Preliminary Amendments and Remarks herein are intended to respond to the Official Action mailed November 5, 1992.

B. The Rejections Under §112

Claims 1-23 of Serial No. 07/944,505 were rejected under 35 USC §112, second paragraph as being indefinite. Claim 1 and others were rejected for reciting the phrase "support capable of specifically associating with the target under binding conditions." The Examiner determined the phrase is vague and indefinite functional language describing a chemical moiety by what it does rather than by what it is structurally so that it is impossible to know what is and what is not claimed. Claim 6 was rejected for its use of the term "probe". The Examiner determined this usage is vague and indefinite. The Examiner asked whether Applicants intend a specific nucleic acid sequence which will probe through hybridization or whether something else is intended. Claim 6 was also rejected for being phrased in functional language.

Claim 10 was rejected for reciting the term transcriptase. This use was said to be vague and ambiguous. The Examiner asked whether reverse transcriptase was intended? Claim 11 and others were rejected for reciting the phrase "non-specific oligonucleotide primer." Claim 13 and others were rejected for their use of the phrase "substantially separating." These phrases were said to be vague and indefinite.

Claim 21 was rejected for its use of the phrase "capable of binding to a retrievable support." The claims were rejected for reciting the phrase "retrievable support." These phrases were also said to be vague, indefinite and functional language. In addition, the Examiner determined it is not clear what support would not be retrievable so that this usage is confusing. The claims were also rejected for their usage of the phrase "reagents adapted to be applied to said removal product." This phrase was said to be vague and indefinite.

Claims 22 and 23 were rejected for reciting the phrase "the method of Claim 21." The Examiner noted that Claim 21 is to a kit rendering Claims 22 and 23 confusing. Claim 23 was also rejected for its use of the phrase "capable of interacting with a magnetic field." This phrase was said to be vague and indefinite in light of the known ability of any carbon, nitrogen or hydrogen containing compound to interact with a magnetic field (citing NMR). The Examiner determined it is not clear what Applicants are describing.

C. The Rejections Under §103

Claims 1-23 were rejected under 35 USC §103 as unpatentable over Mullis U.S. No. 4,683,202 when taken with any one of Moss, Stabinsky or Engelhardt and taken further in view of Ranki, Josephson or Schroder if necessary.

Mullis was said to teach DNA amplification and point out the great value of this method for improved sensitivity and improved ability to isolate specific nucleotide sequences. It was admitted, however, that Mullis does not specifically teach nucleic acid affinity chromatography prior to the amplification reaction. At the same time, all of the secondary references were said to teach the well known method of affinity chromatography, both with nucleic acid attached to a support (direct hybridization) as well as through ligands attached to one strand of nucleic acid (e.g., biotin-avidin). The secondary references were further said to teach the value of affinity chromatography in its ability to isolate specific nucleotide sequences and remove unwanted sequences which

would interfere with later usefulness of the sequences. The secondary references also teach the greater efficiency of hybridization and improved sensitivity of an affinity purified sample compared to a non-purified sample (citing Moss, Fig. 3), although the Examiner asserted this fact would be well known to one of ordinary skill in the art. It would be obvious, the Examiner concluded, for one of ordinary skill to combine the teachings of the primary reference (Mullis) which show improved sensitivity and improved ability to purify a sequence with the secondary references which teach a method providing improved ability to purify a sequence and improved sensitivity since the methods are all directed to the same result and one of ordinary skill would expect an improvement in results.

As to claims directed to association with a "probe," the Examiner asserted it is not clear what is meant by this language (apparently referring to the prior discussion under §112). However, the Examiner continued, it appears to be the well known method of sandwich hybridization (citing Ranki) which also claims increased sensitivity and greater ability to isolate specific sequences.

As to claims reciting "non-specific oligonucleotide primer," the Examiner asserted it is not clear what is meant by this language. At the same time, however, the Examiner asserted that it appears that Applicants are simply referring to the well known method of random primer polymerization which is used to label probes. The Examiner asserted this method is well known not only as an efficient method of making a second copy (into which label nucleotides can be added) but is also more efficient than using a single primer. The Examiner concluded one of ordinary skill in the art would have known this technique and would have been motivated to use it since it makes a second strand thereby doubling the number of copies to be amplified.

As to claims using a "bead capable of interacting with a magnetic field," the Examiner asserted it is not clear what it meant by this language. At the same time, however, the Examiner asserted it appears to be the well known method of Josephson and Schroder for magnetic separations.

As to the kit claims, the Examiner concluded it would have been obvious to one of ordinary skill in the art to package all of the components in a kit for the convenience of practitioners of the method.

For clarification, the Examiner stated it as his position that Applicants simply

combined the well known method of nucleic acid amplification with the equally well known method of affinity chromatography to produce a result which would have been expected and with sufficient motivation to make the combination. The Examiner concluded Applicants' invention would have been prima facie obvious to one of ordinary skill in the art at the time of the invention.

Finally, the Examiner noted that Wood, Noyes and Shih are merely cumulative to the teachings of Moss, Stabinsky, Engelhardt and that the two other Mullis references were merely cumulative to Mullis.

D. The Restriction Requirement

The Examiner reminded Applicants that the application was subject to a restriction requirement whereby Applicants were directed to elect from between the claims of Group I (Claims 1-23) and Group II (Claim 24). The Examiner further reminded Applicants that they had provisionally elected tc prosecute the claims of Group I. Finally, the Examiner instructed Applicants that they must affirm their provisional election of Group I in responding to the Office Action mailed November 5, 1992.

III. Applicants' Invention

Before addressing Applicants' amendments and the merits of the Official Action mailed November 5, 1992 for Serial No. 07/944,505, Applicants believe it would be useful to describe the invention disclosed and claimed in the subject application.

Applicants' invention pertains to improved methods and kits for use in capturing, amplifying and detecting target molecules. Embodiments of the invention provide methods for rapid, sensitive detection of nucleic acid targets present in clinical samples. The invention permits capture, amplification and detection of DNA and RNA targets present in clinical samples in extremely small amounts and with great sensitivity. The invention couples target amplification techniques with noise reduction techniques to provide a detection method of great sensitivity. At the same time, the invention permits the production of large amounts of purified target polynucleotides. Diagnostic embodiments of the invention are readily adaptable to automation and a variety of labeling techniques.

Nucleic acid hybridization is well known for its utility in assays for the detection of various pathogens and diagnosis of various diseases. The invention extends this utility into regimes of assay sensitivity previously unavailable to the practitioner. The invention advances nucleic acid hybridization methods by combining target purification methods with target amplification methods. Nucleic acid targets can be amplified using any of a variety of methods. These include the polymerase chain reaction PCR. However, although PCR was introduced with the promise of great specificity for target amplification, the reality is that PCR is not as specific as practitioners require. Due to nonspecific binding of PCR primers, PCR will often amplify nucleic acids other than the nucleic acid of interest.

Applicants have found that target purification methods can be applied prior to target amplification to insure that only the intended target polynucleotides are amplified. More fundamentally, minute amounts of target polynucleotides can be amplified exponentially in substantially purified form.

IV. Applicants' Response To The Official Action Mailed November 5, 1992 For Serial No. 07/944,505

A. Applicants' Amendments

Applicants would request entry of the amendments submitted herewith. Applicants have cancelled Claims 1-24 and replaced them with new Claims 25-50. The new claims are submitted to overcome the rejections made in the November 5, 1992 Office Action for Serial No. 07/944,505. At the same time, the new claims feature the various embodiments of the invention described supra. Applicants' amendments add no new matter to the application.

B. Response To Restriction Requirement

U.S. Serial No. 07/944,505 was subject to a restriction requirement. The invention was restricted into two have groups. Group I contained Claims 1-23; Group II contained Claim 24. Applicants had previously provisionally elected to prosecute the claims of Group I. Thereafter, Applicants were directed to affirm their election in responding to the Office Action mailed November 5, 1992. Applicants would hereby affirm their provisional election to prosecute the claims of Group I.

C. Response To Rejections Under §112

As described, previously, Claims 1-23 were rejected Under 35 USC §112, second paragraph as indefinite. Applicants traverse all of these rejections as inapplicable to the newly added claims and overcome as to Claims 1-23 because these claims have been canceled. More specifically, Claim 1 and others were rejected for reciting the phrase "support capable of specifically associating with the target under binding conditions." The Examiner determined the phrase is vague and indefinite. Although Applicants do not necessarily agree with the Examiner's determination, the rejection is now unfounded because the phrase is not included in the claims now under consideration.

Claim 6 was rejected for its use of the term "probe." The Examiner asked whether Applicants intend a specific nucleic acid sequence which will probe through hybridization or whether something else is intended. Claim 6 was also rejected as phrased in functional language, presumably for its recitation of the phrase "support is capable of associating with the target through a probe." Applicants submit this phrase is nowhere used in the claims now under consideration. Therefore, this part of the rejection of Claim 6 is now unfounded. Applicants submit the rejection as to Applicants' use of the term "probe" is clearly misplaced. Applicants have specifically defined the term "probe" at page 1, line 36 - page 2, line 3 of the specification. Additionally, Applicants have disclosed numerous examples of probes throughout the application (See, e.g., page 23, line 17 et seq and figure 2; page 28, line 10 et seq and figures 4-6; page 35, line 16 et seq. and the examples). In light of these, Applicants submit their use of the term "probe" is not vague and indefinite and request that this rejection be withdrawn.

Claim 10 was rejected for reciting the term "transcriptase." The Examiner asked whether "reverse transcriptase" was intended. Applicants note that the term transcriptase generally applies to a DNA dependent RNA polymerase and the term reverse transcriptase generally applies to an RNA dependent DNA polymerase. Therefore, the terms "transcriptase" and "reverse transcriptase" generally apply to different polymerases. (See, e.g., Dictionary of Biochemistry of Stenesh, Wiley - Interscience (1975).) Applicants also note that the use of transcriptase is disclosed in the specification at page 2, line 35 - page 3, line 2. Similarly, the specification discloses the use of reverse transcriptase at page 29, lines 6-10. Accordingly, Applicants' amended claims recite the use of both transcriptase

and reverse transcriptase. Applicants further submit their use of the term transcriptase is not vague and indefinite. Applicants respectfully request that this rejection be withdrawn.

Claim 11 and others were rejected for reciting the phrase "non-specific oligonucleotide primer." While Applicants do not necessarily agree with the rejection, Applicants submit the rejection is inapplicable to the amended claims because these claims do not recite the phrase. Accordingly, Applicants request that the rejection be withdrawn.

Claim 13 and others were rejected for their use of the phrase "substantially separating." Applicants submit the rejection is misplaced. Applicants have disclosed the use of retrievable supports in the methods and kits of their invention. These retrievable supports can be particles, grains, beads or filaments capable of dispersion within and separation from a medium (See page 11, lines 26-29). Magnetic beads are preferred as retrievable supports (See; page 9, line 16 et seq.). Applicants submit that it is reasonable and accurate to describe the separation of such supports as "substantially separating." Applicants submit that those with skill in the art will have no difficulty in understanding Applicants' use of the phrase in the claims. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claim 21 was rejected for its use of the phrase "capable of binding to a retrievable support" and "retrievable support." Applicants submit the rejections are misplaced. Applicants have specifically defined the terms "retrievable" (page 2, lines 13-16) and "support" (page 2, lines 17-19) in the specification. Additionally, Applicants have identified numerous examples of retrievable supports in the specification such as magnetic beads (page 9, line 17 et seq.) particles, grains or filaments capable of dispersion and separation from a medium (page 11, lines 26-32). Applicants submit that those skilled in the art will have no difficulty in understanding what is meant by "retrievable support" in light of these express definitions and numerous examples. Accordingly, Applicants request that this rejection be withdrawn. Additionally, while Applicants do not necessarily agree with this rejection, Applicants note that the amended claims do not recite the phrase "capable of binding to a retrievable support." Therefore, Applicants submit the rejection is inapplicable to the amended claims and request that it be withdrawn.

Claim 21 was also rejected for its use of the phrase "reagents adapted to be applied to said removal product." Again, while Applicants do not necessarily agree with this

rejection, Applicants note that the phrase is not used in the amended claims. Accordingly, Applicants submit the rejection is inapplicable to the amended claims.

Claims 22 and 23 were rejected for reciting the phrase "method of Claim 21." The Examiner noted that Claim 21 is to a kit. Applicants submit that this rejection is inapplicable to the amended claims and request that it be withdrawn.

D. Response To Rejections Under §103

As described supra, Claims 1-23 were rejected under 35 USC §103 as obvious. In concluding the rejection, the Examiner took the position that Applicants have simply combined the well known method of nucleic acid amplification with the equally well known method of affinity chromatography to produce an expected result. The Examiner further asserted the art provided sufficient motivation for the combination. The Examiner concluded the invention would have been prima facie obvious to one of ordinary skill at the time it was made. Applicants traverse these rejections. Applicants submit no proper prima facie argument for obviousness can be made out and that in purporting to do so the Examiner misapplied the teachings of the cited references, ignored other teachings within the primary references which teach away from Applicants' invention and did not consider the teachings of other references, not of record, which evidence that the invention addresses a problem present in the art but not solved by others prior to Applicants' invention.

Claims 1-23 were rejected as unpatentable over Mullis (U.S. No. 4,683,202) when taken with any one of Moss, Stabinsky or Engelhardt and taken further in view of Ranki or Josephson or Schroder if necessary. Wood, Noyes and Shih were said to be cumulative to Moss, Stabinsky and Engelhardt. Mullis (U.S. No. 4,683,195) and Mullis (Cold Spring Harbor Symbosia) were said to be cumulative to Mullis (U.S. No. 4,683,202).

Mullis was said to teach DNA amplification and point out the great value of this method for improved sensitivity and improved ability to isolate specific nucleotide sequences. The Examiner admitted Mullis does not specifically teach nucleic acid affinity chromatography prior to amplification. The secondary references were cited for teaching various aspects of affinity chromatography in general and the value of affinity chromatography in isolating specific sequences from unwanted sequences. Moss was

particularly cited for teaching that greater hybridization efficiency and improved sensitivity could be obtained for an affinity purified sample in comparison to an impure sample. The Examiner concluded it would be obvious to combine the teachings of Mullis (improved sensitivity and improved purification) with the secondary references (improved purification and improved sensitivity) since the methods are all directed to the same result and one of ordinary skill would expect an improved result.

Applicants submit the Examiner's conclusion is the product of an improper picking and choosing of selective disclosure from the cited references to obtain Applicants' invention and that when the references are considered for all that they teach the references do not disclose or suggest Applicants' invention. For example, while it is true that Mullis (U.S. No. 4,683,202) discloses DNA amplification and some improved sensitivity and ability to isolate specific nucleotide sequences, Mullis also teaches away from Applicants' invention. Specifically, Mullis teaches:

> The present invention obviates the need for extensive purification of the product from a complicated biological mixture.

(Col. 2, lines 32-34). Mullis reaffirmed this teaching later in the disclosure:

> It is not necessary that the sequence to be amplified be present initially in a pure form; it may be a minor fraction of a complex mixture ... or a portion of a nucleic acid sequence due to a particular microorganism which organism might constitute only a very minor fraction of a particular biological sample.

(Col. 5, lines 49-56). Plainly, Mullis teaches that the amplification method of his invention does not include purification before amplification and, in fact, does not require purification. Thus, Mullis teaches away from Applicants' invention.

At the same time, however, Mullis recognized that non-target background nucleic acids might also be amplified in addition to the intended target nucleic acids (See Example 10 at Col. 25, line 23). To the extent Mullis recognized this as a problem, Mullis taught the use of nested sets of primers to decrease this background. Mullis did not disclose or suggest Applicants' method for reducing this background but proposed another method instead. Thus, Mullis' own disclosure belies the Examiner's conclusion of obviousness.

The secondary references do not bridge the gap between Mullis' disclosure and

Applicants' invention. Moss, Stabinsky and Engelhardt do not disclose or suggest amplification of or detection of amplified nucleic acids. Accordingly, none of them even considers problems such as noise resulting from amplification of nonspecifically bound nucleic acids or solutions to such problems. None of them discloses any reason to ignore the teachings of Mullis that Mullis' invention "obviates the need for extensive purification of product from a complicated biological mixture" (U.S. No. 4,683,202 at Col. 2, lines 32-34). Thus, Moss, Stabinsky and Engelhardt do not disclose or suggest Applicants' invention alone or in combination with Mullis.

Similarly, Ranki does not disclose or suggest amplification of nucleic acids. Neither does Ranki consider the significance of nonspecifically bound nucleic acids to an amplification process. Thus, Ranki too does not disclose or suggest Applicants' invention alone or in combination with Mullis.

Josephson and Schroder were cited for disclosing their methods for magnetic separations. However, these references do not address amplification of nucleic acids, problems associated therewith or solutions thereto. They do not disclose or suggest Applicants' invention alone or in combination with Mullis and the other cited references.

Wood, Noyes and Shih were cited as cumulative of Moss, Stabinsky and Engelhardt and not for any new teaching absent from these previously discussed references. Applicants' own review of Wood, Noyes and Shih found no additional teaching which renders Applicants' invention unpatentable alone or in combination with the other cited references.

The Examiner cited numerous references in attempting to establish a prima facie case of obviousness against Applicants' claimed invention. Although Applicants think it plain that the Examiner did not make out a valid prima facie case, Applicants believe the shortcomings of the Examiner's arguments become more apparent when the actions of those skilled in the art are considered. As demonstrated herein, those with skill in the art have incorporated target amplification by PCR into hybridization techniques and have recognized that such processes are more problematic to use than touted by Mullis (U.S. No. 4,683,202) and do require measures to avoid amplification of nucleic acids other than the designated targets. Those with skill in the art did not combine the teachings of the cited references in the manner proposed by the Examiner to obtain Applicants' claimed

invention. Applicants submit the inability of those in the art to resolve problems attendant to the use of PCR in hybridization assays as Applicants have done is compelling evidence of the unobviousness of Applicants' invention. This is discussed more fully below.

As discussed previously, Applicants' invention principally serves to enhance the sensitivity of nucleic acid hybridization assays utilizing target amplification. Targets can be amplified by a number of ways including PCR. Applicant's invention enhances sensitivity by eliminating from the amplification medium extraneous (nonspecific) nucleic acids which might otherwise be amplified by PCR thereby introducing noise into the assay. The problem of nonspecific amplification is real as evidenced by the reports in the references enclosed herewith. For example, as noted at page 1154 of Schochetman.[2] (Appendix 3):

> [PCR] amplified sequences of target DNA can be detected by a variety of methods. If enough amplified DNA is present, it can be visualized after gel electrophoresis and ethidium bromide staining; however, this method cannot provide definitive identification.... This is particularly true if the target sequence initially is present in extremely small quantities, a situation that may lead to amplification of some nonspecific sequences and yield too little specific DNA to be visualized. (emphasis added)

Similarly, Vosberg noted at page 4 (Appendix 4):

> However, uncontrolled biochemical sample compositions and a high degree of DNA and RNA complexity have the disadvantage of reducing reaction specificity .... Random primer target interactions cannot be excluded.

Vosberg proposed other methods for enhancing such specificity.

At page 144 of PCR Protocols (Appendix 5), the authors urged Judicious Selection of Controls:

> The cloning of amplified product is a case in point. Often, the amount of target generated from an amplification is insufficient for direct cloning and requires reamplification of the target. To minimize reamplification of nonspecific products, the band of interest is first separated on a gel, excised, eluted ... and used to reseed a subsequent amplification. Each of these additional steps can potentially result in cross-contamination and thereby jeopardize the authenticity of the result. (emphasis added)

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[2]The cited passages are marked for identification in the appendices.

Coutlée (Appendix 6) reported similar concerns. In discussing the use of Taq DNA polymerase at page 246, Coutlée reported: "Increased specific and non-specific amplifications were observed with higher quantities of Taq and longer extension times." In discussing identification of amplified products using radio-labelled deoxy-nucleotide triphosphates, Coutlée also noted that "nonspecific bands can sometimes comigrate at the same level as the specific band" (at page 247).

Finally, in U.S. No. 5,374,524, to Miller (Appendix 7) confirms:

> A disadvantage of [PCR] is that the detection of the nucleic acids produced, using a direct assay method, is complicated in that the amplification process can produce nucleic acid sequences which are not faithful copies of the original nucleic acid which was to be copied. These erroneous nucleic acid sequences can provide false positives in the assay which increase the background noise and thus decrease the sensitivity of the entire method.

(See Col. 2, lines 2-10). Miller's solution to this problem is to apply sandwich hybridization techniques following amplification by PCR. Applicants submit that utilization of their invention and target purification prior to amplification overcomes the same concerns identified by Miller and permits detection by other methods in addition to sandwich hybridization. Thus, Applicants' invention provides a more versatile solution to the problems identified by Miller and the other skilled workers cited herein.

Applicants submit that the problem of nonspecific binding is real and substantial for assays seeking ever greater sensitivity. Moreover, as evidenced by those working with PCR, Mullis is simply wrong in stating that PCR eliminates the need for extensive purification.

Applicants also submit the Examiner has overlooked certain advantages in the invention which demonstrate unobviousness. In particular, Applicants' invention simplifies the selection of primers for PCR. As noted by Cahill at page 1483 (Appendix 8), it is well known that "[p]rimer optimization and selection is an empirical process. Each primer pair must be evaluated for sensitivity and specificity by use with actual samples." However, Applicants' invention permits more general primers to be used in the PCR process thereby avoiding the concerns expressed earlier and, at the same time, simplifying many PCR

applications. This is discussed more fully at page 56, lines 22-33 of Applicants' specification.

Applicants' invention overcomes the undeniable problem of nonspecific amplification in PCR based amplification. The invention provides the additional and unexpected advantage of enabling the use of more general primers in the PCR amplification and, therefore, assays utilizing PCR amplification. Applicants submit the Examiner's prima facie case of obviousness reflects more an improper hindsight determination based on Applicants' own teachings than a proper evaluation of what the cited references do teach and those with skill in the art have found to be true. Applicants submit their claimed inventions are patentable and in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

December 5, 1995

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"Express Mail" mailing label number EM256990425 US
Date of Deposit December 5, 1995
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231
Lisa Evans
December 5, 1995

20210209062560

Notice of Allowability

Application No.	Applicant(s)
08/238,080	Collins et al.
Examiner	**Group Art Unit**
Dianne Rees	1807

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to *7/10/97,7/14/97*.

☒ The allowed claim(s) is/are *25-50 and 53-66*.

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☒ Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☒ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. 22.

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal lettter addressed to the Official Draftsperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Interview Summary, PTO-413

☐ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☒ Examiner's Statement of Reasons for Allowance

Interview Summary

Application No.	Applicant(s)
08/238,080	Collins et al.
Examiner	**Group Art Unit**
Dianne Rees	1807

All participants (applicant, applicant's representative, PTO personnel):

(1) *Dianne Rees* (3) _____

(2) *Norvall Galloway* (4) _____

Date of Interview *Oct 13, 1997*

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☒ was reached. ☐ was not reached.

Claim(s) discussed: *all pending*

Identification of prior art discussed:

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
Discussed that Applicant's Executed Declaration and Terminal Disclaimer had been received and matched to the Application and that the case was now in condition for allowance

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. ☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☒ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

DETAILED ACTION

1. The following is an examiner's statement of reasons for allowance:

The claims are drawn to methods of PCR amplification wherein the target is first separated from the sample by using a support that binds to the target polynucleotide and then amplified. In further embodiments of the invention a probe is contacted to a target and the target probe complexes then contacted to the support which binds to the probe and the support and complex are separated from the medium, The probe target complex is then leased into a second medium and substantially separated from the support and the target is subsequently amplified..The instant application has priority to 10/23/86

The closest prior art is Vary et al and Henson et al. Vary et al teaches a method for amplifying and detecting a target polynucleotide in a sample comprising amplifying the target polynucleotide by primer extension, immobilizing the amplified polynucleotide on a support , separating the amplified polynucleotide and detecting said polynucleotide. Vary et al does not teach binding a target polynucleotide to the support prior to amplification and does not teach retrievable supports. Henson et a teaches general methods of isolating a target sequence of interest from a sample by immobilization onto a solid support and that the order of reaction

between a single stranded nucleic acid and a probe and a support may be varied according to experimental needs. However, the art at the time of filing did not recognize that the efficiency of PCR amplification would decrease due to the presence of contaminants in a sample and therefore provided no motivation to purify a target sample from a heterogenous sample of nucleic acids prior to amplification. Having not recognized the problem, applicant's solution therefore, while utilizing routine methodology to modify PCR amplification techniques, would not have been obvious at the time that the invention was made. The Declaration of Dr. David Pershing,further supports this conclusion as providing further evidence concerning the skill of the art at the time of filing , attesting that one of skill in the art would likely stay away from combining a hybridization capture method with a PCR method since one would not be motivated to provide a method with the potential to lose target nucleic acids prior to amplification.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dianne Rees whose telephone number is (703) 308-6565.

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
10/14/97

Dianne Rees
October 13, 1997
10/13/97

Interview Summary

Application No.	Applicant(s)	
09/533,906	Collins et al	
Examiner	Group Art Unit	
Diana Johannsen	1655	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Diana Johannsen*

(2) *Carla Myers*

(3) *Cecilia Tsang*

(4) *Jean B. Fordis*

(5) Norval B. Galloway

(6) David J. Lane

Date of Interview *Jan 16, 2001*

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

by FAX to 202/408-4400

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☐ was reached. ☒ was not reached.

Claim(s) discussed: *all pending*

Identification of prior art discussed:

See attachment.

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:

See attachment.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. ☐ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's Interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Diana J

1/16/01

DIANA JOHANNSEN
PATENT EXAMINER
ART UNIT 1655

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

Attachment to Interview Summary

Prior art discussed.

PCR Technology (H.A. Erlich, ed., Stockton Press 1989, pp. 1-5), PCR Protocols (M.A. Innis et al, eds., Academic Press 1990, pp. 13-19), Mangiapan et al (J. Clin. Microbiol. 34:1209 [1996]), Hill (IVD Technology 6:36 [2000]), Brown et al (Ann. Rev. Biochem. 43:667 [1974]), Rabinow (Making PCR, Univ. Chicago Press 1996, p. 9), Arsenyan et al (Gene 11:97 [1980]), Boss et al (J. Biol. Chem. 256(24):12958 [1981]), Gaubatz et al (Biochim. Biophys. Acta 825:175 [1985]), Powell et al (Cell 50:831 [1987]).

Comments on discussion.

Ms. Fordis presented an overview of the invention and described advantages provided by target capture that were not appreciated in the art as of the time of filing of the present application (specifically, separation of target molecules from contaminants/inhibitors of amplification), referring to teachings in the Erlich and White references that target purification prior to amplification is unnecessary. Ms. Fordis discussed the 1996 Mangiapan reference, which was cited during the prosecution of the '338 patent and which presents sequence capture PCR as a new development. It was agreed that applicants consider 12/21/1987 to be the priority date to which they are entitled with respect to the pending claims. Ms. Fordis noted that the protest filed in the case ignores problems of sample processing that are discussed in, e.g., the Hill reference.

Ms. Fordis argued that the high levels of amplification and amplification "*in vitro* by an efficient DNA polymerase" discussed on page 687 of the Brown reference were not possible at the time of the Brown reference (1974), and that the Brown reference would have led one to have employed cloning rather than some type of *in vitro* amplification. Dr. Lane noted that, from 1975 to the early 1980's, cloning was the "method of choice" to obtain copies of a nucleic acid target, and Ms. Fordis referred to the Rabinow reference in support of this. Ex. Myers noted that while unexpected results related to improvement of PCR by separation of targets from contaminants were relied upon in the allowance of the '338 patent, the instant specification does not make reference to PCR or to any advantage related to removal of contaminants/inhibitors. Dr. Lane noted that all enzymatic amplification techniques would be subject to inhibitors, although the particular types of inhibitors might vary. Ms. Fordis referred to col 13 of the '338 patent, noting that the invention was described as providing increased sensitivity, and Mr. Galloway noted that a number of types of *in vitro* amplification are disclosed in the specification. In response to a question from Ex. Myers, it was noted by applicants representatives that the advantages provided by removal of inhibitors would be advantageous in both specific and non-specific capture and amplification methods. It was noted that in embodiments in which specific capture probes are employed, one advantage of the present invention is the ability to amplify captured targets either specifically or non-specifically. Ex. Myers inquired as to whether any advantages other that contaminant/inhibitor removal were provided by target capture *per se*. Ex. Johannsen noted that the specification appeared to provide basis for the amendments presented in the reissue

application, and that the specification provided basis for both specific and non-specific amplification of targets subsequent to capture. Ex. Johannsen noted the breadth of the kit claims, and noted that it did not appear that the kit claims had been separately addressed in the '338 application or in the reissue application to date. It was further noted that the kit claims would have to be examined anew, independent of the method claims (i.e., method step limitations cannot be read into the kit claims). The breadth of the term "amplification" was discussed, with Ex.'s Myers and Johannsen noting the breadth of the definition at col 2, and Ms. Fordis arguing that this definition cannot be read alone, and that the totality of the claims and specification (including col 15-16 and examples 4-7) make clear that the term as used in the claims is limited to *in vitro* amplification. Ex. Myers noted that the reissue claims (e.g. claim 41), in reciting the limitation "*in vitro* amplification", might suggested that the independent claims are intended to encompass both *in vivo* and *in vitro* amplification. Ms. Fordis noted that the claims include additional limitations (e.g., to production of a "multitude" of "polynucleotide amplification products"). Ms. Fordis noted that the issue of priority raised in footnote 8 of the protest (and discussed in footnote 19 of the response) relates to a different group of applications and not to the present case. Ms. Fordis briefly discussed the Arsenyan, Boss, Gaubatz, and Powell references, noting that these references do not anticipate the *in vitro* amplification methods of the present invention, as discussed in the response to the protest. Ms. Fordis noted that a supplemental IDS will be submitted by the week of 1/22/01. It was agreed that Ms. Fordis and Ex. Johannsen will be in contact early next week, prior to action on the case by Ex. Johannsen. It was further agreed that

applicants may submit, within the next week or two, additional information/arguments with respect to the new issues raised by Ex.'s Myers and Johannsen prior to action on the reissue application.

EXHIBIT H

IN THE UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

- - - - - - - - - - - - - -X

GEN-PROBE INCORPORATED,

Plaintiff,

VS.

VYSIS, INC.,

Defendant.

- - - - -- - - - - - - - X

NO.99cv2668 H (AJB)

CONFIDENTIAL

Videotaped Deposition of
JONATHON MICHAEL LAWRIE, Ph.D.
Durham, North Carolina
Thursday, February 15, 2001

Reported by:
Sydney C. Silva, Registered Professional Reporter
File No:

COPY

disclosed and claimed in the 338 patent is limited to any particular type of amplification? 17:38:44 17:38:48

MR. BOWEN: Objection, calls for a legal conclusion. 17:38:50 17:38:53

A. You know, it's limited to the definition we had in there for amplification so it was in vitro, for example. 17:39:05 17:39:08 17:39:13

Q. Do you believe the invention disclosed and claimed in the 338 patent is limited to the use of nonspecific amplification? 17:39:17 17:39:19 17:39:25

MR. BOWEN: Objection, calls for a legal conclusion. Leading. 17:39:28 17:39:30

A. No, it's not limited to nonspecific amplification. 17:39:39 17:39:43

Q. Now earlier today Mr. Bowen focused you on some portions of the specification at Column 30. Do you have the 338 patent in front of you, Exhibit 37? If you could look at Column 30? 17:39:45 17:39:49 17:39:54 17:39:59

Specifically it's Column 30, starting at Line 30, where it says, "Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ nonspecific enzymes or primers." Do you see that? 17:40:13 17:40:15 17:40:19 17:40:22 17:40:25

A. Yes. 17:40:27

CERTIFICATE OF REPORTER

STATE OF NORTH CAROLINA)
COUNTY OF MECKLENBURG)

I, Sydney C. Silva, Notary Public within and for the State of North Carolina, do hereby certify:

That JONATHON MICHAEL LAWRIE, Ph.D., the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true record of the testimony given by the witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 23rd day of February, 2001.

SYDNEY C. SILVA
Notary Public in and for the
State of North Carolina

My Commission expires May 16, 2001.

20270290 9062E360

CONFIDENTIAL - ATTORNEYS' EYES ONLY

VOLUME: I

PAGES: 1-191

EXHIBITS: 115-132

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

- x

GEN-PROBE INCORPORATED,

Plaintiff,

v. C.A. NO.

VYSIS, INC., 99CV2668 H (AJB)

Defendant.

- x

CONFIDENTIAL - ATTORNEYS' EYES ONLY

DEPOSITION of JAMES C. RICHARDS

March 30, 2001

9:51 a.m.

Westin Hotel

70 Third Avenue

Waltham, Massachusetts

Reporter: Michael D. O'Connor, RPR

Q. What follows in the four or five sentences after that CIP --

A. Right. -- is describing the subject matter of the CIP, isn't it?

A. This would have been conversations with Janiuk or something like that, as I said, verbal discussions. I didn't read this thing.

Q. You didn't read what?

A. This application. I asked Tony -- see, we had a file, the MOI file, and this was in it, and it was something we needed to pursue, along with the others that were in this letter.

Q. The four or five sentences that follow after the statement that a CIP application was filed about a year later --

A. Yes.

Q. -- was your understanding of the method of amplification taught in the CIP application; is that correct?

A. Say that question again.

Q. The details of the amplification process that are set forth there, that's your understanding of the amplification method set forth in the column CIP that claimed target

CERTIFICATE

Commonwealth of Massachusetts

Suffolk, ss.

I, Michael D. O'Connor, Registered Professional Reporter and Notary Public in and for the Commonwealth of Massachusetts, do hereby certify that JAMES C. RICHARDS, the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true record of the testimony given by the witness.

I further certify that I am neither related to or employed by any of the parties in or counsel to this action, nor am I financially interested in the outcome of this action.

In witness whereof, I have hereunto set my hand and seal this 2nd day of April, 2001.

Michael D. O'Connor

Notary Public

My commission expires

October 26, 2001

COPY

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Attorneys for Defendant VYSIS, INC.

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

DECLARATION OF DR. DAVID H. PERSING IN SUPPORT OF VYSIS' OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

I, David H. Persing, declare as follows:

1. I have personal knowledge of the facts set forth herein, and if called as a witness would testify to the truth thereof.

2. I am presently Vice President, Molecular Biology, at Corixa Corporation, and Medical Director, Infectious Disease Research Institute, both in Seattle, Washington. I received a Ph.D. (Department of Biochemistry and Biophysics) and an M.D. (School of Medicine) from the

University of California, San Francisco in 1988. My Ph.D. work was performed in the laboratory of Nobel laureate Harold Varmus. I was a Resident and Research Fellow at the Yale School of Medicine from 1988-1990. I was employed by the Mayo Clinic, Rochester, Minnesota from 1990 to 1999. My work has been primarily directed to the study of infectious diseases, including study of the application of nucleic acid hybridization assays in medical diagnostics. I was director from 1993 to 1999 of the Molecular Microbiology Lab of the Mayo Clinic, which was one of the premier centers for the diagnosis of infectious diseases by molecular methods. There, I pioneered techniques for pathogen discovery and contamination control, and discovered several new pathogens. I am a member of three Scientific Advisory Boards, including the Scientific Advisory Board of Vysis, Inc., and am an Editor-in-Chief of the reference text Diagnostic Molecular Microbiology PRINCIPLES AND APPLICATIONS. A list of my patents and scientific publications is included in my curriculum vitae attached as Exhibit A.

3. I have extensive experience in the fields of nucleic acid hybridization and amplification. I have been familiar with and been a practitioner of nucleic acid hybridization assays and various amplification techniques used with nucleic acid hybridization assays since about 1985. As indicated in Exhibit A, I have a number of scientific publications relating to these techniques.

4. I have been retained as an expert by Vysis in this lawsuit. In that regard, I have reviewed the claims, specification, and pertinent prosecution history of U.S. Patent No. 5,750,338 ("'338 patent"). My involvement in the patent application that became the '338 patent goes back to 1997 when I submitted a declaration to the United States Patent & Trademark Office relating to the unobviousness of the combination of target capture prior to amplification as disclosed and claimed by the '338 patent. A copy of my July 9, 1997 Declaration is attached hereto as Exhibit B.

5. The '338 patent discloses and claims a method for detecting a target nucleic acid (polynucleotide) in a sample by performing target capture and then amplifying the target nucleic acid. Target capture is a procedure involving binding (hybridizing) a target nucleic acid in a sample to a support and separating the bound target from the sample. Amplification is an *in vitro* technique for making multiple copies of the target nucleic acid to enable the target nucleic acid to be detected. By targeting a portion of the nucleic acid of an organism such as a virus or bacterium, for example,

the method of the '338 patent enables the presence of the target organism to be detected in a sample such as blood, even if the organism is present in very small amounts. Among other advantages, target capture purifies the sample by removing non-target materials such as contaminants and inhibitors that can interfere with the amplification step. By separating the target from the sample prior to amplification, the invention of the '338 patent enables effective removal of these contaminants and inhibitors from the system enabling amplification to proceed optimally.

6. I have read the Declaration of Dr. Joseph Falkinham In Support of Gen-Probe's Motion For Partial Summary Judgment and disagree with the conclusions presented in paragraphs 5 and 52 of that Declaration. Specifically, I disagree with Dr. Falkinham's conclusions that as of December 21, 1987, a person of ordinary skill in the art (a) would have understood the term "amplifying" as used in the claims of the '338 patent to mean amplifying any nucleic acid sequence present in the sample only by the use of non-specific amplification methods described in the '338 patent, and (b) would not have understood the term "amplifying" to mean amplifying by use of sequence-specific amplification methods.

7. For the reasons pointed out below, it is my opinion from my review of the '338 patent claims, specification, and prosecution history that those of ordinary skill in the art in December 21, 1987 would have understood the term "amplifying" in the claims of the '338 patent to include specific types of amplification methods, and would not have understood that term as used in the patent to be limited to non-specific types of amplification methods.

8. First of all, there is nothing from the context of the '338 patent specification that would have led those of ordinary skill in the art in December of 1987 to believe that the inventors meant to limit their invention to non-specific types of amplification. Performing non-specific amplification after target capture would have been a much more challenging approach to molecular diagnostics in 1987 than performing specific amplification after target capture. That is because non-specific amplification techniques amplify all of the nucleic acid in a sample, both target and non-target nucleic acid. Specific amplification techniques, in contrast, are intended to amplify only the target nucleic acid. Thus, if target capture could be shown to purify the target nucleic acid in a sample sufficiently so that non-specific amplification would allow detection of the target nucleic acid

with the attendant benefits discussed above in paragraph 5, then those of ordinary skill in the art in December 1987 would have certainly understood that target capture followed by specific amplification would also successfully do so to achieve these same benefits.

9. In addition, in my opinion the particular language used in the '338 patent specification would not have indicated to those of ordinary skill in this field that the inventors wanted to exclude specific amplification from the invention. It is my understanding that the '338 patent application was a continuation-in-part application of an earlier application that was directed only to target capture techniques. The primary discussion of the invention of combining target capture with amplification begins at column 30, line 15 of the '338 patent. The first sentence defines the invention broadly by stating that "[t]he sensitivity of the above DNA or RNA target capture methods can be enhanced by **amplifying** the captured nucleic acids." (Emphasis added.) The specification then describes a particular benefit of the invention, that "[t]his **can be** achieved by non-specific replication using standard enzymes . . . ." (Emphasis added.) It is important to note that the specification does **not** say that enhanced sensitivity of the target capture methods **is** achieved by non-specific amplification, but rather it says that it **can be** achieved by non-specific amplification. In so stating, the specification sets a minimum requirement for amplification specificity, but does not indicate that more specific amplification methods should be excluded.

10. The specification then again describes the invention as including amplification generally in the paragraph at column 30, lines 23-29. The paragraph following this describes both specific and non-specific amplification, but points out the particular benefits of the invention when using non-specific amplification:

> Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, **can** employ non-specific enzymes or printers (i.e. enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence). Although any background, non-target, nucleic acids are replicated along with target, this is not a problem because most of the background nucleic acids have been removed in the course of the capture process. Thus **no specially tailored primers are *needed*** for each test, and the same standard amplification reagents can be used, regardless of the targets.

Col. 30, lines 30-40, emphasis added.

11. The paragraph quoted above points out that the use of target capture in accordance with the invention makes it possible to use non-specific primers (i.e., non-specific amplification). Without the use of target capture prior to amplification, non-specific amplification would not be a viable technique for detecting target nucleic acids in a sample because, as pointed out in the quoted paragraph, non-specific amplification causes the replication of virtually any nucleic acid sequence, including other irrelevant nucleic acids in the sample. However, because the invention of the '338 patent provides a target capture step that removes background, non-target nucleic acids from the sample prior to amplification, this is not a problem. The specification thus points out that no specially tailored primers (used in specific amplification) are **needed** for each test. The specification does not state that one would not want to use specially tailored primers, only that such primers are not needed in this invention. Thus, an important advantage of the invention is that, because of the preceding target capture step, either specific or non-specific amplification can be successfully used in nucleic acid detection assays; whereas without the invention, only specific amplification could be used.

12. The disclosure at column 30, lines 15-40 of the '338 patent specification tells me and those of ordinary skill in the art that while the use of target capture made it possible to use non-specific amplification in assays for detecting nucleic acids, the invention was more generally directed to the use of target capture prior to either specific or non-specific amplification. The benefits of the invention, i.e., purifying the sample by removing non-target materials such as contaminants and inhibitors that can interfere with the amplification step, would be obtained with both specific and non-specific amplification, especially since it is now widely recognized that even the most specific amplification methods comprise a degree of non-specificity. If the inventors had wanted to limit the invention to non-specific amplification, I believe they would not have drafted the text of the application as they did.

13. I also disagree with Dr. Falkinham's statements in his declaration that "the primers described in the ['338] patent are not pre-selected to bind to specific nucleotide sequences as part of the amplification process" and that Example 5 describes only non-specific amplification. See paragraphs 14 and 31, respectively. To the contrary, Example 5 of the '338 patent does disclose the

use of a specific primer. In particular, while Example 5 states initially that random oligohexamer primers can be used to achieve non-specific amplification, Example 5 also discloses that "[a]lternatively, the double stranded DNA can be formed by synthesis starting from capture probe a." Col. 31, lines 48-49. In this instance, the capture probe acts as the primer. Since the capture probe binds specifically to the target DNA, the capture probe would be a specific primer to the target. This is an example of specific amplification because the primer, capture probe a, binds to a specific, unique DNA sequence in the target organism.

14. I have also reviewed the prosecution history of the '338 patent. In my opinion, the correspondence between the applicants for the '338 patent and the Patent Office leads to the inescapable conclusion that both the applicants and the Patent Office (no fewer than five different Patent Office Examiners) considered the claimed invention to encompass the polymerase chain reaction ("PCR"), which is a type of specific amplification.

15. Patent Examiner Scott A. Chambers, Ph.D, and Primary Patent Examiner Amelia Burgess Yarbrough cited the basic Mullis PCR patents in rejecting the claims of the '338 patent application in the first Official Action by the Patent Office. July 20, 1990 Office Action (Paper No. 2) in application serial no. 07/136,920, pages 3-4. Clearly, if the Patent Examiners had believed that the claims of the '338 patent application were limited to non-specific amplification, it would have been illogical for them to have cited the PCR patents against the application, because PCR is a type of specific amplification. Then, Examiner Chambers and Primary Examiner Margaret Moskowitz continued to cite the Mullis PCR patents against the pending patent claims. March 12, 1992 Office Action (Paper No. 2) in application serial no. 07/644,967, page 3; November 5, 1992 Office Action (Paper No. 3) in application serial no. 07/944,505, page 3. In responding to rejections of the pending claims based on the Mullis PCR patents, the owner of the '338 patent never attempted to distinguish the Mullis patents by arguing that Mullis disclosed specific amplification, whereas the invention of the '338 patent was directed to non-specific amplification. To the contrary, the patent owners repeatedly emphasized that the invention included PCR-type amplification:

> Applicants' invention principally serves to enhance the sensitivity of nucleic acid hybridization assays utilizing target amplification. **Targets can be amplified by a number of ways including PCR**. Applicant's invention enhances sensitivity

> by eliminating from the amplification medium extraneous (nonspecific) nucleic acids which might otherwise be amplified by PCR thereby introducing noise into the assay.

Page 18 of December 5, 1995 Preliminary Amendment and Response to Restriction Requirement (Paper No. 8) (responding to November 5, 1992 Office Action in application serial no. 07/944,505), page 18, emphasis added.

16. If the patent owner had considered the invention to be limited to non-specific types of amplification, I believe it would have argued this to the Patent Office to overcome the rejection of the patent claims over the Mullis PCR patents. Instead, the patent owner maintained all along that the invention encompassed PCR and argued that the invention was not obvious in view of the PCR patents.

17. In fact, the owner of the '338 patent was able to obtain allowance of the patent claims by convincing the Patent Office, *inter alia*, that the invention of including a target capture step to purify a sample prior to PCR amplification would not have been obvious to those of ordinary skill in the art as of the filing date of the original application. Patent Examiner Dianne Rees, Ph.D., and Primary Patent Examiner W. Gary Jones make it clear in the very first sentence of their Examiner's Statement of Reasons for Allowance that these Examiners considered the claims of the '338 patent to encompass specific amplification techniques such as PCR:

> The claims are drawn to methods of **PCR amplification** wherein the target is first separated from the sample by using a support that binds to the target polynucleotide and then amplified.

Page 2 of October 16, 1997 Notice of Allowability (Paper No. 23), emphasis added.

18. In my opinion, the only reasonable conclusion one can reach after reading the prosecution history of the '338 patent is that both the applicants for the '338 patent and the five patent examiners who examined the patent application believed that the term "amplify" in the patent claims included specific amplification.

19. In my opinion, for the reasons pointed out above, those of ordinary skill in the art as of December 21, 1987 reading the specification of the '338 patent would conclude that the term "amplify" as used in the claims of the '338 patent includes specific amplification. It is also my opinion from my review of the prosecution history of the '338 patent that both the applicants and the

patent examiners considered the invention to encompass specific amplification techniques such as PCR. For these reasons as well as the fact that the claims simply recite the term "amplify," I believe the '338 patent claims include specific types of amplification.

I hereby declare under penalty of perjury under the laws of the United States of America that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. This declaration was executed by me on this 25th day of May, 2001 at Seattle, Washington.

David H. Persing

Curriculum Vitae

David Harold Persing, M.D., Ph.D.

Date of Birth:	June 13, 1955, San Jose, California
Home Address:	22401 NE 25th Way, Redmond, WA 98053
Work Address:	Seattle Life Sciences Center, Suite 200 1124 Columbia St. Seattle, WA 98104
Contact Information:	206-754-5879 (V) 206-754-5715 (F) (Work) 425-898-0754 (V) 425-898-0274 (F) (Home) E-mail: persing@corixa.com
Marital Status:	Married
Education:	September 1974 - June 1979 California State University, San Jose, California B.A. in Biochemistry awarded June 1979

October 1980 - May 1988
School of Medicine, University of California, San Francisco

October 1981 - May 1988
Medical Scientist Training Scholarship Program, University of California, San Francisco

September 1982 - March 1987
Graduate Program in Biochemistry and Biophysics, Division of Genetics, University of California, San Francisco

March 1988
Ph.D. granted, Department of Biochemistry and Biophysics, University of California, San Francisco

May 1988
M.D. granted, School of Medicine, University of California, San Francisco

July 1988 - June 1990
Resident and Fellow, Department of Laboratory Medicine, Yale School of Medicine

July 1989 - September 1990. Research Fellow, Department of Cell Biology, Yale School of Medicine

Honors:

Graduation with highest honors, California State University, San Jose, California, 1979

Departmental Honors in Chemistry, 1979

Finalist, Dean's Prize for Research, School of Medicine, 1981

Graduate Dean's prize for Student Research, University of California, San Francisco, 1984

Gip A. Hudson Award for the study of liver diseases, National Student Research Forum, Galveston, Texas, 1985

James McLaughlin Award for the study of infectious diseases, National Student Research Forum, Galveston, Texas, 1985

University of California Patent Funds Award, 1986

Young Investigator Award, Academy of Clinical Laboratory Physicians and Scientists, 1989

Mayo Foundation Scholar, 1990

ASM Foundation Lectureship, 1995-1997

Justus Strom Award, Swedish Medical Society, 1997

Research Sponsor, Naomi Judd Liver Scholar Award, American Liver Foundation, 1997

Olof Norlander Memorial Lecture, Karolinska Institute, 1998

Dubious Honors:

Consultant to Criminal Attorney Barry Scheck and invited expert witness, O.J. Simpson criminal trial

Committee/Editorial Appointments:

NCCLS Subcommittee on Molecular Methods, 1993-4
NCCLS Subcommittee on Lyme Disease Testing, 1997
College of American Pathologists, Microbiology Resource Committee, 1994-present
Associate Editor: *Journal of Clinical Microbiology*, 1996-present
Associate Editor: *Molecular Diagnosis*, 1996-present
IDSA Practice Guidelines Committee on Lyme Disease, 1997-present

Editorships:

Journal of Clinical Microbiology (1996-present)

Editorial Boards:

Journal of Clinical Microbiology (1990-1997)
Diagnostic Microbiology and Infectious Diseases (1994-97)
New England Journal of Medicine (Regular Reviewer)
Gastroenterology (Regular Reviewer)
Journal of Infectious Diseases (Guest Reviewer)
Emerging Infectious Diseases (1997-present)

Scientific Advisory Boards:

Vysis, Inc., Naperville, IL (1995-present)
BioMerieux, Marcy L'Etoile, France (1996-1999)
Roche Molecular Systems, Alameda, CA (1998-present)

Corporate Boards:

Virologic, Inc, South San Francisco, CA (2000-)

Licensure and Certification Status:

Medicine and Surgery License #35080, State of Minnesota
Board Certified Forensic Examiner
Board Eligible, Clinical Pathology
New York State Laboratory Certification in Bacteriology, Virology, Parasitology, and Laboratory Immunology

Intellectual Property:

"Specific Detection of Rifampin Resistant *Mycobacterium tuberculosis* by Nucleic Acid Amplification," U.S. patent granted July 1997. European patents pending.

"Sensitive and Specific Detection of *B. burgdorferi* by Nucleic Acid Amplification," patent pending since 1994. Technology licensed to two licensees.

"Method for Detecting *Borrelia burgdorferi* Infection," U. S. patent issued in 2000.

"Recombinant proteins for immunologic detection of granulocytic ehrlichiosis." U.S. patent pending since 1997.

"Recombinant proteins for immunologic detection of human babesiosis." U.S. patent pending since 1997

"Method for long-term preservation of nucleic acids"
U.S. patent pending since 1997 (claims allowed April 2001)

"Toll-like receptor activation and stimulation of innate immune responses via aminoalkyl gluocosaminide phosphates"

Appointments:

Summer Research Fellowship, University of California, San Francisco, School of Medicine, 1980

September 1981 to May 1988:
Medical Scientist Training Program, University of California, San Francisco

July 1988 to June 1990:
Resident, Department of Laboratory Medicine, Yale University School of Medicine

July 1990 to September 1990:
Mayo Foundation Scholar, Department of Cell Biology, Yale University School of Medicine

September 1990 to June 1994:
Senior Associate Consultant, Divisions of Clinical Microbiology, Experimental Pathology and Infectious Diseases, Mayo Clinic/Foundation

June 1994 to July 1999:
Consultant, Divisions of Clinical Microbiology, Experimental Pathology and Infectious Diseases, Mayo Clinic/Foundation

January 1991 to June 1995:
Assistant Professor, Department of Laboratory Medicine and Pathology, Mayo Medical School

July 1995 to July 1999
Associate Professor of Microbiology, Mayo Medical School, Mayo Clinic/Foundation

July 1995 to July 1999
Associate Professor, Department of Laboratory Medicine and Pathology, Mayo Medical School

September 1991 to 1999
Adjunct Professor, Department of Biology/ Microbiology, University of Wisconsin-La Crosse

1996 to July 1999
M.D. - Ph.D. Program Council, Mayo Medical School

August 1999- present
Vice president, Diagnostics Development, Corixa Corporation
Medical Director, Infectious Disease Research Institute
Seattle, WA

Societies:

American Association for the Advancement of Science
American Society for Microbiology
American Society of Tropical Medicine and Hygiene
North Central Cancer Treatment Group

Teaching Experience:

Teaching Assistant, Chemistry for Engineers, San Jose State University, September 1979 to June 1980

Graduate Teaching Assistant, Introductory Biochemistry
UC San Francisco, September 1982 to April 1983

Instructor, Biochemistry National Boards Review Course, School of Dentistry, UC San Francisco, 1983-1986

Biochemistry Advisor, Health Science Special Services Summer Program, 1984-1986

Laboratory Instructor, Medical Microbiology Course, Yale School of Medicine, 1988-1989

Lecturer, Medical Microbiology Course, Yale School of Medicine, 1988-1989

Medical Microbiology Course, Mayo Medical School,

Graduate Immunology Course, "Infection and Immunity," 1993-present.

Graduate Tumor Biology Course, "Infection, Immunity, and Cancer," 1996-1999

Volunteer Services:

Department of Public Health, Huehuetenango, Guatemala, 1977-1978

National Ski Patrol, Alpine Meadows and Homewood, CA, 1978-1981

Dorothy Day House, Rochester, MN

Extracurricular Activities:

Skiing, vintage automobile restoration, brass ensemble (trombone)

Research Experience and Supervisors:

Spring 1979 - Summer 1980
Dr. Robert Fowler, Department of Biology, San Jose State University. Mutational specificity of the base analogue, 2-aminopurine in *Escherichia coli*.

Summer 1980 - Spring 1981
Dr. Phillip Coffino, Department of Microbiology, UC San Francisco. Mechanism of 2-aminopurine mutagenesis in mouse T-lymphosarcoma cells.

Summer 1981 - Fall 1981
Dr. Harold E. Varmus, Department of Microbiology, UC San Francisco. Molecular analysis of mutant *src* alleles.

Summer 1982 - Winter 1983
Dr. Patrick O'Farrell, Department of Biochemistry, UC San Francisco. Isolation and characterization of DNA clones representing the *engrailed* locus of *Drosophila melanogaster*.

Spring 1983 to 1988
Drs. Donald Ganem and Harold Varmus (thesis co-advisors) Identification and characterization of the presurface proteins of hepatitis B virus.

July 1989 to September 1990
Dr. Ari Helenius, Department of Cell Biology, Yale School of Medicine. Papovavirus: assembly, disassembly, and cellular interactions.

Current Research Interests:

Laboratory-based intramurally and extramurally funded programs

1) Immunological interactions of tick-borne infections
2) Effects of T cell differentiation on disease expression
3) Identification and characterization natural immunomodulatory components
4) Stimulation of innate immunity by natural and synthetic microbial products

Clinical research

1) Host immunogenetic determinants of infectious disease expression
2) Pathogen discovery by broad-range amplification techniques
3) Association of infections with cancer and other chronic human diseases
4) Antigen discovery and antigen characterization in human cancer

Extramural Support:

NIH - Allergy and Infectious Diseases
1-PO1-AI30548-01-A1 (9/1/91 - 8/31/96)
Lyme Disease: Pathogenesis and Protection
(Yale Program Project Grant)
P.I.: S. W. Barthold, D.V.M., Ph.D.
Co-investigator: David H. Persing, M.D., Ph.D.
$295,407 award amount, direct costs

NIH - Allergy and Infectious Diseases
1-R01-AI32403-01 (9/30/91 - 8/31/97)
Multilocus Molecular Detection of B. burgdorferi
P.I.: D. H. Persing, M.D., Ph.D.
$1,006,775 total award amount, direct costs

NIH - Arthritis Institute
1-R01-AR41497-01 (9/1/91 - 8/31/95)
Molecular Diagnosis and Monitoring of Lyme Disease
P.I.: D. H. Persing, M.D., Ph.D.
Co-funded with 1-RO1-AI32403-01
$227,359 award amount, direct costs
Status: decision not to renew

Centers for Disease Control
U50/CCU510343- (4/15/94 - 2/1/98)
Genetic Diversity of B. burgdorferi in the United States
P.I.: D. H. Persing, M.D., Ph.D.
$410,365 total direct costs

Centers for Disease Control
U50/CCU510528 (11/1/97 - 10/31/00)
Recombinant Immunoassays for Detection of Babesia microti Infection
P.I.: David H. Persing, M.D., Ph.D.
$187,500, total direct costs

NIH - Allergy and Infectious Disease
1-R01-AI45253-01 (9/30/94-9/29/99)
Animal Models for Chronic Lyme Disease
P.I.: Stephen W. Barthold, D.V.M., Ph.D.
Co-investigator: David H. Persing, M.D., Ph.D.
Co-investigator portion: $683,114 total direct costs

NIH - Allergy and Infectious Disease
1-R01-AI41103-01
Investigation of the Natural History of Babesiosis
(5/1/97 - 4/31/00)
$143,914 per year, direct costs

NIH - Allergy and Infectious Disease
1-R01-AI41103-01 supplement (1/1/98 - 12/31/01)
Investigation of the Natural History of Babesiosis- supplement for Manuel Moro, DVM, Ph.D.
$156,230 total direct costs

Active support:

NIH-National Cancer Institute
1RO1-CA-79429 (6/01/99-5/31/04)
Cancer Chemoprevention-Role of Infection and Immunity
PI: Loprinzi, Charles
Role on project: Coinvestigator (5% salary support)
$27,841 total direct costs

NIH-National Cancer Institute
Epstein-Barr virus in postmenopausal breast cancer
PI: Cerhan, James
6/01/00-05/31/02
Role on project: Coinvestigator (5%)
$134,280 total direct costs

NIH-NIAID
2-R44-AI41840-03
Novel antigens for the serodiagnosis of human babesiosis
09/30/99 – 09/29/01
PI: Houghton, R
Coinvestigator (15%)
$745,853 total costs

NIH-National Cancer Institute
2-R44-CA75794-02
Novel genes for the diagnosis and prognosis of breast cancer
PI: Houghton, R
8/14/00 - 7/30/02 (10%)
$767,046 total costs

Defense Advanced Research Projects Agency (DARPA)
"Immune modulation by topical administration of synthetic lipid A analogues"
Principal Investigator (25%)
$3,649,412 over two years, total costs
Program starts 5/01/01

Pending Support at IDRI:

NIH - Allergy and Infectious Disease
2-R01-AI41103
Principal Investigator
Investigation of the Natural History of Babesiosis
$143,914 per year, direct costs

NIH- Allergy and Infectious Diseases
New R01 submission-NHLBI
Principal Investigator
Detection and characterization of cryptic B. microti infection in blood donors.

Pending Support at Corixa:

Books:

1. **Persing DH**, Smith TF, White TJ, Tenover F (eds). Diagnostic Molecular Microbiology: Principles and Applications, ASM Press, Washington, DC, 1993.

2. **Persing DH** PCR Protocols for Emerging Infectious Diseases, ASM Press, Washington, DC. 1996.

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Book Chapters & Reviews:

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(12 additional articles submitted or in press)

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-- PATENT APPLICATION --
-- Attorney Docket No. 25,835.11 --

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	M. L. Collins, et al.
Serial No.:	08/238,080
Filing Date:	May 3, 1994
Title:	TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS
Art Unit:	1807
Examiner:	Dianne Rees, Ph.D.

DECLARATION OF DAVID H. PERSING, M.D., PH.D.

I, David H. Persing, M.D., Ph.D., declare and state as follows:

1. I am director of the Molecular Microbiology Lab of the Mayo Clinic, Rochester Minnesota. I have been employed by the Mayo Clinic since 1990. My work has been directed to the study of infectious diseases and includes the study of the application of nucleic acid hybridization assays in medical diagnostics.

2. I am a member of the Scientific Advisory Board of Vysis, Inc. I understand Vysis is a wholly owned company of Amoco Corporation, the owner of the subject patent application.

3. A copy of my curriculum vitae is attached as Exhibit 1. Briefly, I have been involved in molecular microbiology research since about 1978. Our laboratory is currently one of the premier centers for the diagnosis of infectious diseases by molecular methods. Our lab has pioneered techniques for pathogen discovery and contamination control, and has discovered several new pathogens as a result.

4. A list of my scientific publications is attached as Exhibit 2.

5. I have been provided with and have reviewed copies of the following documents:

(a) Patent Application U.S. Serial No. 08/238,080 entitled Target And Background Capture Methods With Amplification For Affinity Assays naming Collins et al. as inventors;

(b) A document entitled Preliminary Amendment And Response To Restriction Requirement dated December 5, 1995;

(c) U.S. Patent No. 4,851,331 entitled Method And Kit For Polynucleotide Assay Including Primer-Dependant DNA Polymerase naming Vary et al. (the "Vary patent") as inventors;

(d) European Patent Publication No. 0 139 489 entitled Sandwich Hybridization Method For Nucleic Acid Detection naming Hansen (the "Hansen" application) as the inventor;

(e) European Patent Publication No. 0 159 719 entitled Hybridization Method For the Detection Of Genetic Materials naming Rabbani et al. (the "Rabbani" application) as inventors;

(f) A transmittal letter from the Patent Office and accompanying Office Action Summary dated June 20, 1996;

(g) A transmittal letter from the Patent Office and accompanying Office Action Summary dated January 17, 1997; and

(h) The article "Sequence Capture-PCR Improves Detection of Mycobacterial DNA in Clinical Specimens," by Mangiapan et al., J. Clin. Microbiol., 34(5): 1209-1215 (1996).

6. I have reviewed claims 25 and 31 as presented in the Preliminary Amendment. I am informed that the inventions claimed in these claims were made on or before December 21, 1987.

7. I have been familiar with and been a practitioner of nucleic acid hybridization assays and various amplification techniques used with nucleic acid hybridization assays since about 1985. I have generally followed the literature of assay methods using nucleic acid hybridization since about 1985. As indicated in Exhibit 2, I have published a number of publications relating to these techniques and am a Editor-in-Chief of the reference text **Diagnostic Molecular Microbiology** PRINCIPALS AND APPLICATIONS.

8. I have been asked to consider whether the methods recited in claims 25 and 31 would have been obvious to those practicing in the field of nucleic acid hybridization assays and utilizing techniques for amplifying nucleic acids such as the polymerase chain reaction or PCR in light of the Vary patent, the Hansen application and the Rabbani application. In my opinion, the methods recited in claims 25 and 31 would not have been obvious to such practicioners in light of these references.

9. The Vary patent discloses a method for assaying for polynucleotides using primer dependent DNA polymerase. More particularly, the patent discloses

> a method for the determination of a target nucleotide sequence in the nucleic acid of a biological [sample] which comprises the steps:
> (a) contacting the sample with a probe polynucleotide of a sufficient length under conditions sufficient for the probe polynucleotide to bind to the target nucleotide sequence and form a hybrid having a double-stranded portion including the 3' end of the probe polynucleotide, with the sample nucleic acid strand extending in a 3' to 5' direction beyond the 3' end of the probe polynucleotide;
> (b) extending the probe polynucleotide strand of the hybrid beyond its 3' end in the 5' to 3' direction on the sample nucleic acid strand by incorporating nucleoside triphosphates from solution, a plurality of the nucleotides incorporated into the extended probe strand being detectably-modified nucleotides; and
> (c) detecting detectably-modified nucleotides which have been incorporated into probe polynucleotide strand as a measure of target nucleotide sequence in the biological sample. (Col. 1, line 54 - col. 2, line 6)

The primary feature of the invention is the selective incorporation of detectably labeled nucleotides into an elongation segment formed on a sample polynucleotide containing a target nucleotide sequence as a template and as an extension of a probe polynucleotide (which need not be labeled, but may contain a site for specific immobilization) as primer. (Col. 1, lines 47 - 53) More generally, the patent discloses a method for detecting a target polynucleotide in a sample comprising hybridizing a primer to the target polynucleotide, extending the primer, immobilizing the double-stranded polynucleotide product of the primer extension on a support, separating the double-stranded polynucleotide on the support from the sample and detecting the amplified polynucleotides. The double-stranded polynucleotide is then immobilized on a solid support and detected. Preferably, the double-stranded polynucleotide is separated from the sample for detection. (Col. 4, line 6 et seq.)

The patent does not disclose or suggest immobilizing and separating the target polynucleotide from the sample prior to hybridization of the primer to the target or primer extension.

Moreover, it is not even clear that the patent discloses amplification as that term is generally understood in the art and as is intended by claims 25 and 31. Target amplification generally means increasing the number of target polynucleotides manifold, typically exponentially. For example, amplification of nucleic acids by the polymerase chain reaction (PCR) follows primer extension with separation of the double-stranded primer extension product into single-stranded polynucleotides and repeating the process steps (hybridization of primer to target polynucleotide, primer extension and separation of the double-stranded product into more single-stranded polynucleotides) thereby increasing the population of detectable target polynucleotides exponentially. The Vary patent discloses only a single primer extension and detection of the extension product. Thus, in absolute terms, the number of polynucleotides actually detected by Vary's method can be no more than the number of target polynucleotides initially present in the sample. In contrast, the number of polynucleotides detected following target amplification can easily be more than a million times greater than the number of polynucleotides initially present in the sample.

10. The Hansen application discloses a method for detecting specific nucleic acids by providing the nucleic acid to be detected in single-stranded form and thereafter contacting it with a labeled nucleic acid probe specific for a given section of the nucleic acid strand. Additionally, a biotinylated nucleic acid probe specific for a different portion of the nucleic acid strand, is bonded to an avidin coated microparticle. The strand having the labeled probe hybridized to it is then mixed with the avidin coated microparticles. The probes are allowed to bind to the target nucleic acid so that the target becomes bound to the microparticle. The microparticles are then separated from the sample. The coupling of biotin to avidin is sufficiently strong that the targets remain bound to the microparticles and so are separated from the sample with the microparticles. The bound material is then assayed for the presence of the label signalling the presence of the target polynucleotide. (Page 2, lines 14 -33) The application discloses that the order of reaction among the assay components may be varied to suit the needs of the investigator. (Page 6, lines 17-21) The primary feature of the application appears to be the use of the strong binding characteristics of biotin and avidin in facilitating the separation of the target from the sample prior to detection. The application does not disclose or even consider target amplification as a part of its methods.

11. The Rabbani application discloses methods for the detection of target genetic material having a desired base sequence or gene, mutations and the deletion of a gene or base. The methods are based upon techniques which utilize two labeled single-stranded polynucleotide segments which are complementary to the same or opposite strands of the target material. These methods result in the formation of double or multi-hybrids. The multi-hybrids are detected by means of various labels. The application does not disclose or even consider target amplification as a part of its methods.

12. I have reviewed the arguments made by the Examiner in concluding that claims 25 and 31 as presented in the Preliminary Amendment are obvious in view of the Vary patent and the Hansen and Rabbani applications. I disagree with the Examiner's conclusion for the following reasons. As noted above, none of these references discloses any real teachings regarding the use of amplification in a nucleic acid hybridization assay. Accordingly, I believe it is inappropriate for the Examiner to apply the disclosure of these references to the use of amplification techniques for enhancing assay sensitivity. Although it may appear obvious today to apply these references as the Examiner has done, I believe that to do so overlooks or greatly oversimplifies the problems actually encountered by practitioners attempting to obtain highly sensitive assays using target amplification. I do not believe the methods of claims 25 and 31 were obvious in light of these references in December 1987.

It is necessary to keep in mind that the inclusion of target amplification to nucleic acid hybridization assays adds an additional, significant level of complexity to assay methodology. Additional materials are required; additional process steps are required; additional time is required; and additional cost is required to add amplification to conventional (unamplified) assay methodology. Those working with nucleic acid hybridization assays had no real incentive to add to their methods the complexity attendant to amplification unless the object targets were expected to be present in levels below the detection level of their conventional methods.

As techniques such as PCR were developed for amplifying nucleic acids, those practicing hybridization assays sought to incorporate the new amplification techniques into their methods. Initially, users and proponents of PCR believed that PCR was highly specific and could be made to selectively amplify the desired target in an otherwise complex sample system. Practitioners believed that adequate specificity could be imparted to the amplification by careful selection of the primers used in the amplification so that additional steps for isolating target prior to amplification were not required. Since the addition of such isolation steps would be costly and time consuming, would further complicate the assay and was generally believed to be unnecessary; those who were adding amplification to their nucleic acid hybridization assays had a strong incentive to avoid the addition of target

isolation steps to their hybridization assays. It was not until much later that it became apparent that non-specific amplification was occurring despite the careful selection of primers, i.e., that even careful selection of primers would not permit the selective amplification of a particular nucleic acid. I believe this realization did not occur until after December 1987.

13. I believe there is another reason why practicioners of hybridization assays were reluctant to use hybridization techniques to purify their intended targets from the initial sample system prior to amplification. This is the lack of complete binding efficiency in the initial target capture step. It is and was generally well understood that the binding efficiency of (capture) probe to target is substantially less than 100%. Thus, in sample systems where the presence of target nucleic acid is already known to be low, the lack of high binding efficiency meant that significantly less than the already low number of targets present in the sample would be captured and survive separation from the sample for amplification, thereby decreasing the already low amount of target available for detection. This concern over the low binding efficiencies of the capture step has persisted as is evidenced at page 127 in the section addressing Target Capture techniques from Chapter 6 of the reference text **Diagnostic Molecular Microbiology** (copyright 1993), attached as Exhibit 3. ("However, to date there are no published studies that demonstrate efficient capture and detection of fewer than 100 target molecules, ...")

Accordingly, I do not agree with the Examiner's conclusion that those incorporating amplification techniques into nucleic acid hybridization assays in or before December 1987 would have concluded that the methods claimed in claims 25 and 31 of the Preliminary amendment were obvious in light of the Vary patent, the Hansen application and the Rabbani application. To the contrary, coupled with the conventional understanding at that time (that careful selection of primers would permit adequate selectivity of the target and specificity in the amplification product), the practitioners' concern regarding imperfect binding efficiencies and the expected loss of real target before amplification occurred reinforced their incentive to avoid further complicating their assays by the addition of target separation steps to their assays.

I do not believe that the concerns of practitioners regarding imperfect binding efficiencies would have been overcome by the disclosure of the Hansen application which addressed a much more simplified assay system. There is nothing in Hanson application, for example, to suggest that practitioners should elect to first separate less than all of the scarce target from the sample before completing the assay.

14. Finally, I would also mention that the methods of Claims 25 and 31 have provided an additional advantage which was unexpected in or before December 1987. This is the elimination of amplification inhibitors normally present in the sample system. For example, as indicated by the article by Mangiapan, many clinical samples contain PCR inhibitors such as hemoglobin and sodium dodecyl sulfate. By separating the target from the sample prior to amplification, Applicants' methods effectively remove these inhibitors from the system enabling amplification to proceed optimally. This has an obvious beneficial effect on the overall assay.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledged that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

8/9/97
Date:

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Attorneys for Defendant VYSIS, INC.

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

DEFENDANT'S STATEMENT OF DISPUTED FACTS IN OPPOSITION TO PLAINTIFF'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

Defendant, Vysis, Inc., respectfully submits the following statement of disputed material facts, together with supporting evidence, in support of its opposition to Plaintiff's Motion for Partial Summary Judgment.

GEN-PROBE ALLEGED UNDISPUTED FACTS	DISPUTED FACTS AND SUPPORTING EVIDENCE
1. United States Patent No. 5,750,338 (the '338 patent) consists of the specification, including drawings, and the claims. The '338 patent contains six independent claims (claims 1, 7, 19, 27, 28 and 34). Each of these claims is generally directed to a method of, or a kit for, amplifying and/or detecting a target polynucleotide (i.e., a nucleic acid), wherein the target is first isolated on a support.	Each of the '338 patent claims recites "amplifying" a target polynucleotide (or sample). The claims require at least the steps of target capture (e.g., binding a support to the target polynucleotide and substantially separating the support and bound target polynucleotide from the sample) and amplification. U.S. Patent No. 5,750,338, cols. 32-36.
2. Each of the claims contains a step of "amplifying" the target polynucleotide or sample. For example, claim 1 provides: 1. A method for amplifying a target polynucleotide contained in a sample comprising the steps of: (a) contacting the sample with a first support which binds to the target polynucleotide; (b) substantially separating the support and bound target polynucleotide from the sample; and (c) *amplifying* the target polynucleotide.	No dispute.
3. The '338 patent specification sets forth seven examples of the methods taught by the inventors. The first three examples refer only to methods of target capture alone, and do not refer to amplification. The last four examples refer to combining target capture and methods	No dispute.

GEN-PROBE ALLEGED UNDISPUTED FACTS	DISPUTED FACTS AND SUPPORTING EVIDENCE
of amplification. Between the end of target capture examples and the start of the amplification examples, the inventors expressly set forth their teachings with respect to amplification methods. Referring to the target capture methods described in Examples 1 through 3, the inventors stated: The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by ***nonspecific*** *replication using standard enzymes* (polymerases and/or transcriptases).	
4. The '338 patent makes it clear that the reference to non-specific amplification methods was intentional and pointed out that one of the express benefits of their invention was that it permitted the use of non-specific enzymes and non-specific primers: Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ **non-specific** enzymes or primers. **Thus no specifically tailored primers are needed for each test, and the same standard reagents can be used, regardless of targets.**	The reference to non-specific amplification was to point out the particular benefits of the invention when using non-specific amplification. Thus, because of the preceding target capture step, either specific or non-specific amplification can be used. Persing Decl., ¶ 11.

GEN-PROBE ALLEGED UNDISPUTED FACTS	DISPUTED FACTS AND SUPPORTING EVIDENCE
5. The '338 patent specification sets forth four examples of the amplification methods contemplated by the inventors (Examples 4-7). Consistent with the teaching of the patent that sequence-specific primers and specific enzymes are not necessary, each example suggests and describes amplification methods that use only non-specific primers and enzymes.	Each example does **not** suggest and describe **only** non-specific primers and enzymes. Example 5 discloses the use of a specific primer. Persing Decl., ¶ 13.
6. Example 4 illustrates "the use of RNA polymerase to amplify target DNA." It describes a method for amplifying the capture DNA by non-specific amplification using polymerases that lack transcriptional specificity.	No dispute.
7. Example 4 discloses only non-specific amplification:	No dispute.
8. Example 5 describes a non-specific amplification method in which the target DNA is replicated using random (*i.e.*, non-specific) primers and non-specific transcription of that DNA into RNA: In this example, both non-specific replication of target DNA and transcription of that DNA are used to amplify capture target DNA... . . Because the primers are *random*, some will, simple (sic) as a matter of statistics, bind to and cause	Each example does **not** suggest and describe **only** non-specific primers and enzymes. Example 5 discloses the use of a specific primer. Example 5 discloses that "[a]lternatively, the double stranded DNA can be formed by synthesis starting from capture probe a" Col. 31, lines 48-49 of '338 patent. In this instance, the capture probe acts as the primer. Since the capture probe binds

GEN-PROBE ALLEGED UNDISPUTED FACTS	DISPUTED FACTS AND SUPPORTING EVIDENCE
of statistics, bind to and cause replication of sample sequences, no matter what those sequences are	specifically to the target DNA, the capture probe would be a specific primer to the target. This is an example of specific amplification because the primer, capture probe a, binds to a specific, unique DNA sequence in the target organism. Persing Decl., ¶ 13.
9. Example 5 discloses only non-specific amplification.	For the reasons given above, Example 5 also discloses the use of a **specific** primer. Persing Decl., ¶ 13.
10. Example 6 describes replication of target DNA using DNA polymerase and *random* hexamer oligonucleotides "to bring about *non-specific* double-stranded DNA synthesis" using a series of repeated heat denaturation and enzyme replacement steps	No dispute.
11. Example 6 discloses only *non-specific* amplification.	No dispute.
12. Example 7 describes *non-specific* amplification using an RNA polymerase, Qß replicase: In this example, rRNA and RNA transcribed from target DNA is purified using a capture probe, described above. The hybrid duplex is then denatured and single stranded nucleic acids are then replicated *non-specifically* using Qß replicase…	No dispute.

GEN-PROBE ALLEGED UNDISPUTED FACTS	DISPUTED FACTS AND SUPPORTING EVIDENCE
13. Example 7 discloses only nonspecific amplification.	No dispute.
14. The first pages of the '338 patent provide drawings of various methods encompassed by the invention.	No dispute.
15. The first 3 drawings (Figure 1a to Figure 3) depict target capture methods alone, without amplification.	No dispute.
16. Figures 4, 5 and 6 depict target capture followed by amplification using only non-specific primers or enzymes.	As mentioned, in Example 5, if the double stranded DNA is formed by synthesis starting from capture probe a, this would be use of a specific primer. Persing Decl., ¶ 13.
17. The drawings included in the patent are discussed and described in the text of the patent specification	No dispute.
18. The text of the specification expressly states that in each of the drawings that include amplification (Figures, 4, 5 and 6) "the isolated target is *non-specifically* amplified to form a multitude of amplification products."	As mentioned, in Example 5, if the double stranded DNA is formed by synthesis starting from capture probe a, this would be use of a specific primer. Persing Decl., ¶ 13.
19. One of ordinary skill in the art would have understood the term "amplifying" in the '338 patent to include only the non-specific amplification methods taught by the patent.	Those of ordinary skill in the art as of December 21, 1987 reading the specification of the '338 patent would not have understood the term "amplifying" in the claims of the '338 patent to be limited to non-specific types of

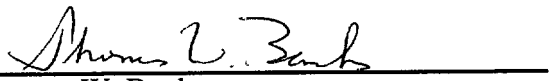
GEN-PROBE ALLEGED UNDISPUTED FACTS	DISPUTED FACTS AND SUPPORTING EVIDENCE
	amplification. Persing Decl., ¶ 7.
20. One of ordinary skill in the art would not have understood the term "amplifying" to include other amplification methods that use sequence-specific primers or enzymes.	Those of ordinary skill in the would have understood that the term "amplify" in the claims includes specific amplification. Persing Decl., ¶¶ 7, 19.
21. The PCR method was first described at a scientific meeting in the summer of 1985 and was published in December 20, 1985.	No dispute.
22. Within the scientific community, PCR was immediately "big news."	No dispute.
23. The patent was meant to cover *new* amplification methods using non-specific primers, not already-known methods such as PCR.	Inventor Lawrie believed that the invention of the '338 patent was not limited to nonspecific amplification. Lawrie Depo., at 262, lns. 8-14, Ex. H to Banks Decl.
24. On December 15, 1989, Dr. James C. Richards, the Director of Business Development and Licensing for Gene-Trak Systems, admitted that the '338 patent encompassed only amplification with non-specific primers and explicitly contrasted the methods of the patent with other methods of amplification using specific primers. Dr. Richards' analysis was set forth in a letter to	Richards said in a document that the "338 patent application claimed non-specific primers or promoters but admitted at his deposition that at the time he wrote the document, he had not read the '338 patent application. Richards Depo, at 184, lns. 7-9, Ex. I to Banks Decl.

GEN-PROBE ALLEGED UNDISPUTED FACTS	DISPUTED FACTS AND SUPPORTING EVIDENCE
one of Gene-Trak's partners, Amoco Technology Company.	
25. Dr. Richards first discussed the fact that the pending patent application encompassed the use of random, non-specific primers. He then discussed the effect of combining non-specific amplification with the use of an initial target capture step. Finally, he pointedly contrasted the invented method with other known methods that used specific primers or promoters (e.g., enzymes): Cetus, Sibia/Salk, Biotechnica, etc. all claim **specific** primers for amplification whereas the present invention claims uses of the opposite, namely, **non-specific** primer or promoters.... Following extensive washing, captured target polynucleotides could be released and the non-specific amplification process could take place.	Richards said in a document that the "338 patent application claimed non-specific primers or promoters but admitted at his deposition that at the time he wrote the document, he had not read the '338 patent application. Richards Depo, at 184, lns. 7-9, Ex. I to Banks Decl.
26. Gen-Probe's HIV-1/HCV Assay use a target-specific amplification technology called Transcription-Mediated Amplification (TMA).	No dispute.
27. TMA uses *specific* primers, *specific* promoters, and a *specific* polymerase enzyme that recognizes only those promoters.	No dispute.

GEN-PROBE ALLEGED UNDISPUTED FACTS	DISPUTED FACTS AND SUPPORTING EVIDENCE
28. Gen-Probe's product does not use non-specific amplification.	No dispute.

Date: May 25, 2001

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.



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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

CASE NO. 99CV 2668H (AJB)

NOTICE OF LODGMENT OF CASE AUTHORITY NOT IN OFFICIAL REPORTER SYSTEM IN SUPPORT OF DEFENDANT VYSIS' OPPOSITION TO GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE that Defendant Vysis, Inc. hereby lodges the following cases that do not appear in the official Federal Reporter system, but which are cited in support of its Opposition To Gen-Probe's Motion For Partial Summary Judgment:

EXHIBIT A: *Synthes v. Depuy Ace Medical Co.*, 1999 U.S. Dist. LEXIS 18173 (E.D. Pa. 1999); and

EXHIBIT B: *Sport Squeeze, Inc. v. Pro-Innovative Concepts, Inc.*, 51 U.S.P.Q. 2d 1764 (S.D. Cal. 1999).

Date: May 24, 2001

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LEXSEE 1999 us dist lexis 18173

SYNTHES (U.S.A.), Plaintiff, v. DEPUY ACE MEDICAL COMPANY COMPANY, Defendant.

CIVIL ACTION NO. 98-2687

UNITED STATES DISTRICT COURT FOR THE EASTERN DISTRICT OF PENNSYLVANIA

1999 U.S. Dist. LEXIS 18173

November 29, 1999, Decided

DISPOSITION:

[*1] Defendant's Motion for Summary Judgment and Plaintiffs' Motion for Summary Judgment both DENIED.

CASE SUMMARY

PROCEDURAL POSTURE: Plaintiff patentee filed a motion for claim construction and summary judgment of infringement and validity of claims for alleged infringement of his patent claim for point contact bone compression plates; defendant, alleged patent infringer, filed a motion for summary judgment of non-infringement or invalidity.

OVERVIEW: Plaintiff patentee was the sole owner of a patent for point contact bone compression plates duly and legally issued by the United States Patent and Trademark Office. Plaintiff accused defendant medical company of infringing his patent in its manufacturing and selling of five different products. Defendant sought summary judgment from the court on the issue of non-infringement or invalidity with regard to the five claims of the patent. Plaintiff opposed defendant's motion with a motion for summary judgment of infringement and validity of claims. In order to grant summary judgment for defendant, the court must have found that no reasonable jury could find that the accused products infringed upon plaintiff's patent in light of the definition of terms. The court denied defendant's motion for summary judgment because it accepted broad definitions of patented components that allowed factual dispute. The court denied plaintiff's motion for summary judgment because there were genuine issues as to material facts concerning defendant's infringement of the patent.

OUTCOME: Court denied summary judgment to both parties; however, there were genuine issues as to material facts concerning the question of infringement by defendant. Therefore, summary judgment was likewise denied to plaintiff patentee.

CORE CONCEPTS

Civil Procedure : Summary Judgment : Summary Judgment Standard

Summary judgment is appropriate only if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law.

Civil Procedure : Summary Judgment : Burdens of Production & Proof

In a motion for summary judgment, the evidence must be viewed in the light most favorable to the nonmoving party.

Civil Procedure : Summary Judgment : Burdens of Production & Proof

Summary judgment may be granted in favor of a defendant on an ultimate issue of fact where the defendant carries its burden of pointing out to the district court that there is an absence of evidence to support the nonmoving party's case.

Patent Law : Infringement : Summary Judgment

The motion of an accused infringer for judgment on the ground of non-infringement of a patent may be granted where the patentee's proof is deficient in meeting an essential part of the legal standard for infringement.

Patent Law : Infringement : Summary Judgment
Patent Law : Infringement : Burdens of Proof
To establish infringement of a patent, every limitation set forth in a claim must be found in an accused product or process exactly or by a substantial equivalent.

Patent Law : Infringement : Summary Judgment
A finding of patent infringement requires that the patent claim cover the alleged infringer's product or process, which in turn necessitates determination of what words in the claim mean.

Patent Law : Infringement : Summary Judgment
A patent infringement analysis involves two steps: proper construction of the asserted claim and then a determination as to whether the accused method of product infringes the asserted claim as properly construed.

Patent Law : Infringement : Claim Interpretation
Civil Procedure : Jury Trials : Province of Court & Jury
The construction of a patent, including terms of art within a claim, are exclusively within the province of the court.

Patent Law : Specification & Claims : Claim Language
Patent Law : Infringement : Claim Interpretation
In determining the proper construction of a patent claim, the court has numerous sources that it may properly utilize for guidance, including both intrinsic evidence, such as the patent specification and file history, and extrinsic evidence, such as expert testimony.

Patent Law : Specification & Claims : Claim Language
Patent Law : Infringement : Claim Interpretation
In interpreting an asserted patent claim, the court should look first to the intrinsic evidence of record, that is, the patent itself, including the claims, the specification and, if in evidence, the prosecution history. Such intrinsic evidence is the most significant source of the legally operative meaning of disputed claim language.

Patent Law : Specification & Claims : Claim Language
Patent Law : Infringement : Claim Interpretation
The court must first look to the words of the claims themselves, both asserted and nonasserted, to define the scope of a patented invention.

Patent Law : Specification & Claims : Claim Language
Patent Law : Infringement : Claim Interpretation
A technical term used in a patent document is interpreted as having the meaning that it would be given by persons experienced in the field of the invention, unless it is apparent from the patent and the prosecution history that the inventor used the term with a different meaning.

Patent Law : Specification & Claims : Description Requirement
Patent Law : Infringement : Claim Interpretation
It is always necessary to review the patent specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning. The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication.

Patent Law : Specification & Claims : Description Requirement
Patent Law : Infringement : Claim Interpretation
Claims must be read in view of the specification, of which they are a part. The specification contains a written description of the invention which must be clear and complete enough to enable those of ordinary skill in the art to make and use it. Thus, the specification is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.

Patent Law : Infringement : Claim Interpretation
Patent Law : Infringement : Prosecution History Estoppel
The court may also consider the prosecution history of the patent. This history contains the complete record of all the proceedings before the Patent and Trademark Office (PTO), including any express representations made by the applicant regarding the scope of the claims. As such, the record before the PTO is often of critical significance in determining the meaning of the claims. Included within an analysis of the file history may be an examination of the prior art cited therein.

Patent Law : Specification & Claims : Description Requirement
Patent Law : Infringement : Claim Interpretation
Varied use of a disputed term in the written description demonstrates the breadth of the term rather than providing a limited definition.

Patent Law : Infringement : Claim Interpretation
A patentee may not proffer an interpretation of a patent claim for the purposes of litigation that would alter the public record.

Patent Law : Infringement : Burdens of Proof
In order to demonstrate anticipation of the patent claims that have allegedly been infringed, the alleged infringer must show, by clear and convincing evidence, that each

and every element of a patent claim is disclosed within a single prior art reference.

COUNSEL:

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For DEPUY ACE MEDICAL COMPANY, DEFENDANT: DONALD E. KNEBEL, BARNES AND THORNBERG, INDIANAPOLIS, IN USA. DANIEL P. ALBERS, BARNES & THORNBURG, INDIANAPOLIS, IN USA. PATRICIA E. CAMPBELL, ALAN K. COTLER, KLETT, LIEBER, ROONEY & SCHORLING, PHILADELPHIA, PA USA. PAUL B. HUNT, BARNES & THORNBURG, SOUTH BEND, IN USA. JOSEPH J. JACOBI, BARNES & THORNBURG, INDIANAPOLIS, IN USA.

JUDGES:

RONALD L. BUCKWALTER, J.

OPINIONBY:

RONALD L. BUCKWALTER

OPINION:

MEMORANDUM

BUCKWALTER, J.

November 29, 1999

Presently before the Court are the Defendant's Motion for Summary Judgment of Non-Infringement or Invalidity and the Plaintiff's Motion for Claim Construction and Summary Judgment of Infringement and Validity of Claims 4 and 14. For the reasons stated below, the Motions are denied.

I. FACTUAL BACKGROUND

Plaintiff Synthes (U.S.A.) ("Plaintiff" or "Synthes") is the sole owner [*2] of United States Patent No. *5,053,036*, entitled "Point Contact Bone Compression Plate" ("the 36 Patent"), which was duly and legally issued by the United States Patent and Trademark Office ("USPTO") on October 1, 1991. Synthes accuses Defendant DePuy Ace Medical Company ("Defendant" or "DePuy") of infringing this patent in its manufacturing and selling of five different products. The 36 Patent is directed to bone compression plates used to stabilize and axially compress broken bones. Compression plates are usually constructed from biologically compatible materials such as titanium alloys, and are provided with screw holes to accept the bones screws which attach the plate to the bone. The bone plate is positioned against the bone, spanning the fracture. Then, holes for the screws are pre-drilled into the bone. Finally, screws are inserted through the holes in the plate and are threaded into the bone, thereby coupling the plate to the bone.

Compression plates were known and used before the issue of the 36 Patent, but according to Synthes, these "prior art" bone plates suffered from certain problems. The main problem was that the plate remained in contact with the underlying bone over [*3] most, if not all, of the area of the lower surface of the plate. According to the 36 Patent's inventors, this condition slowed the healing of bone and reduced the injured body's ability to fight infection. These inventors determined that the problems of the prior art could be overcome by providing a reduced-contact compression plate having a lower surface shaped with cut-outs between the screw holes and a concave lower surface, so as to provide "studs" on its under surface. By providing the plate with studs to serve as bone contact elements, the amount of the bottom surface of the plate that comes into contact with the bone is reduced. This low-contact plate could also be provided with self-compressing screws which result in the bone fragments being axially moved or compressed together.

There are five different DePuy products that allegedly infringe the 36 Patent. The accused products ("Accused Products") are:

- the 3.5 mm Active Compression Plate ("ACP"), also referred to as the Small Fragment ACP, part number 14660.

- the 4.5 mm Narrow ACP, also referred to as the Large Fragment System Narrow ACP, part number 14661.

- the 4.5 mm Broad ACP, also referred to as the Large Fragment [*4] System Broad ACP, part number 14662.

- the hip screw, also referred to as the Barrel Plate or TK2, a plate for use with a hip screw, part number(s) 8015 and/or 8115; and

- the Fibular Composite Plate ("FCP"), part number 8141-13.

In its current Motion, the Defendant asks the Court to grant summary judgment on the issue non-infringement or invalidity with regard to five claims of the 36 Patent. The Plaintiff opposes this Motion and requests summary judgment as to infringement on two of its claims under the 36 Patent.

II. LEGAL STANDARD

Summary judgment is appropriate only "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." *Southwall Techs., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1575 (Fed. Cir. 1995)* (*quoting* Fed.R.Civ.P. 56(c)). The evidence must be viewed in the light most favorable to the nonmoving party. See *SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1116 (Fed.Cir.1985)* (in banc). Summary judgment may be granted [*5] in favor of a defendant on an ultimate issue of fact where the defendant carries its burden of "pointing out to the district court that there is an absence of evidence to support the nonmoving party's case." *Celotex Corp. v. Catrett, 477 U.S. 317, 325, 91 L. Ed. 2d 265, 106 S. Ct. 2548 (1986).*

The motion of an accused infringer for judgment on the ground of non-infringement of a patent may be granted where the patentee's proof is deficient in meeting an essential part of the legal standard for infringement. See *Johnston v. IVAC Corp., 885 F.2d 1574, 1577 (Fed. Cir. 1989).* To establish infringement of a patent, every limitation set forth in a claim must be found in an accused product or process exactly or by a substantial equivalent. See *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1259 (Fed.Cir.1989); Julien v. Zeringue, 864 F.2d 1569, 1571, 9 U.S.P.Q.2D (BNA) 1552, 1553 (Fed.Cir.1989).* Therefore, if DePuy demonstrates to the Court's satisfaction that a reasonable jury could not find that the Accused Products contain every limitation set forth in the claims of the 36 Patent, summary judgment could be [*6] granted in its favor.

A finding of patent infringement requires that the patent claim cover the alleged infringer's product or process, which in turn necessitates determination of what words in the claim mean. See *Markman v. Westview Instruments, Inc., 517 U.S. 370, 134 L. Ed. 2d 577, 116 S. Ct. 1384 (1996).* Therefore, literal patent infringement analysis involves two steps: proper construction of the asserted claim and then a determination as to whether the accused method of product infringes the asserted claim as properly construed. See *Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1581 (Fed. Cir. 1996).* The construction of a patent, including terms of art within a claim, are exclusively within the province of the court. *Marksman. 517 U.S. at 387.* (emphasizing the need for uniform construction of terms within patent claims).

In determining the proper construction of a claim, the court has numerous sources that it may properly utilize for guidance, including both intrinsic evidence (e.g., the patent specification and file history) and extrinsic evidence (e.g., expert testimony). *Vitronics, 90 F.3d at 1581-82.* [*7] It is well-settled that, in interpreting an asserted claim, the court should look first to the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification and, if in evidence, the prosecution history. See *Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995).* Such intrinsic evidence is the most significant source of the legally operative meaning of disputed claim language.

The Court must first look to the words of the claims themselves, both asserted and nonasserted, to define the scope of the patented invention. See *Bell Communications Research, Inc. v. Vitalink Communications Corp., 55 F.3d 615, 620 (Fed.Cir.1995).* A technical term used in a patent document is interpreted as having the meaning that it would be given by persons experienced in the field of the invention, unless it is apparent from the patent and the prosecution history that the inventor used the term with a different meaning. *Hoechst Celanese Corp. v. BP Chems. Ltd., 78 F.3d 1575, 1578 (Fed.Cir.1996).* Second, it is always necessary to review the specification to determine whether the inventor has used any terms [*8] in a manner inconsistent with their ordinary meaning. The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication. *Marksman, 52 F.3d at 979.* As the Federal Circuit has stated, "claims must be read in view of the specification, of which they are a part". Id. The specification contains a written description of the invention which must be clear and complete enough to enable those of ordinary skill in the art to make and use it. Thus, the specification is always highly relevant to the claim construction analysis. *Vitronics, 90 F.3d at 1582.* Usually, it is dispositive; it is the single best guide to the meaning of a disputed term. Id.

Third, the court may also consider the prosecution history of the patent. *Marksman, 52 F.3d at 980; Graham v. John Deere, 383 U.S. 1, 33, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966).* This history contains the complete record of all the proceedings before the Patent and Trademark Office, including any express representations made by the applicant regarding the scope of the claims. As such, the record before the Patent [*9] and Trademark Office is often of critical significance in determining the meaning of the claims. See *Marksman, 52 F.3d at 980.; Southwall Tech., 54 F.3d at 1576* ("The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution."). Included within an analysis of the file history may be an examination of the

prior art cited therein. *Autogiro Co. of America v. United States, 181 Ct. Cl. 55, 384 F.2d 391, 399,* (1967).

III. DISCUSSION

Accordingly, the Court must properly construe the claims that Synthes asserts are infringed by DePuy's accused products. DePuy essentially argues that the accused products do not contain the type of "screw holes" or "studs" as taught by the 36 Patent. If this is the case, then its products would not contain every limitation of the 36 Patent, and summary judgment could be granted for DePuy. Therefore, the Court must determine what is meant by "screw holes" and "studs" and "self-compressing" screw hole in the 36 Patent. In both cases, Synthes argues in favor of a broad construction of the terms, whereas DePuy counters that [*10] the Court should narrowly construe the terms.

1. Term Construction

a. Definition of Screw Holes

DePuy argues that the "plurality of screw holes" limitation of the 36 Patent can only mean "those holes that are capable of fixing or locking the head of a corresponding screw into the bone plate". Therefore, a plurality of such screw holes must mean more than one of these screws.

In the actual claims of the 36 Patent, the screw holes are defined as being "conical and transverse said plate between said upper and lower surfaces such that the narrow end of the cone is towards the lower surface and said holes adapted to receive screws having conical heads of a predetermined cone angle, such that the plate will not slide down the heads of the screws." (Claim 2). Claim 9 describes a plurality of bone screws for attaching the plate of Claim 7 to the bone, and screw holes capable of receiving such screws. Finally, Claim 13 adds a bone plate assembly according to # 9 wherein said screws are of a length that permits engagement of the screw with only one side of the bone cortex. The Court can find no distinct meaning of the "plurality of screw holes" limitation from the language of [*11] the claims alone.

Since the claims themselves do not give a complete answer to the term "plurality of screw holes", the Court must now look to the written specifications of the 36 Patent. Synthes uses the terms "screw holes" in different ways throughout the specification. For example, it uses that term to describe prior art screw holes (Pl. Mem. in Opp., Ex. A, 36 Patent 3:40) n1 . When discussing the proposed reduced contact plate, Synthes uses "screw holes" to define both locking screw holes and self compressing screw holes. See (Pl. Mem. in Opp., Ex. C, Burstein Dep. Tr. 124:12-20) (Def. expert stated that he did not know of and could not imagine a compressing screw hole that is aiso a locking screw hole.) The varied use of the term throughout the specification suggests a broad definition of screw hole consistent with a meaning that encompasses all types of openings through which screws can be passed to attach the plate to the bone. See *Johnson v. Worldwide Assoc., Inc. v. Zebco Corp., 175 F.3d 985, 991 (Fed. Cir. 1999)* (Varied use of a disputed term in the written description demonstrates the breadth of the term rather than providing a limited definition). [*12]

n1 References to the patent specifications are listed in the format of column and then line number. For example, 3:40-45 means Column 3, lines 40-45 of the patent specifications. Within the patent specifications are included the "Claims" of the patent as well as the "embodiments" of the patented technology.

The Defendant argues that it is only through the use of locking screw holes that the Synthes can accomplish its goal of reducing contact between the plate and bone. Synthes does in fact describe a locking screw hole as one manner by which contact can be reduced because it allows the use of short screws that only reach the front cortex of the bone. (Pl. Mem., Ex. A, 3:5-35). However, this is not the only embodiment of the invention that Synthes claims will achieve reduced contact. Alternative methods include the use of a long screw with a spherical or conical insert, and the use of self-compressing screw holes. (Pl. Mem, Ex. A, 3:59-4:15).

The prosecution history of the patent also favors a broad [*13] definition of the plurality of screw holes limitation. Synthes points out that during prosecution of the 36 Patent, the examiners rejected several claims related to the plurality of screw holes limitation as being anticipated by earlier patents. Pl. Mem., Ex. D, page 2. (Treace and Kummer patents disclose plurality of screw holes). The Kummer patent discloses a plurality of 'conventional metallic bone' screws that secure the bone plate to the bone. Pl. Mem., Ex. E, 3:10-15. This Court agrees with Synthes's position that examiner did not view the "plurality of bone screws" as referring only to the locking screw holes, an interpretation that DePuy encourages.

The Court concludes that a "plurality of screw holes" as disclosed in the 36 Patent is entitled to a broad interpretation, a meaning that encompasses all types of openings through which screws can be passed to attach a plate to the bone . In Claim 2, the screw holes are further defined as to be locking and conical. In Claim 4, at least

one screw hole has the additional limitation of being self-compressing. Therefore, the Court can not accept a definition of screws holes that refers only to locking screws.

b. Definition of [*14] "Studs":

The Defendants request that the Court construe studs as " a structure projecting from the undersurface of the plate at the side edge for contact between the plate and bone, such that the area of this contact is reduced to the minimum practicable, and in any case not more than 5% of the total area of the lower surface of the plate". (Def. Mem. at 14). DePuy argues that there is no evidence establishing that any of its Accused Products contain such a limitation or a substantial equivalent thereof, so that it is entitled to summary judgment. Synthes, on the other hand, argues that "studs" means the portion of the lower surface of the plate which provide the reduced contact areas after the plate is screwed down. The term has no requirement that the stud be pointed or that it provide the minimal practicable area of contact with the bone.

Once again, the Court must first look to the claims of the 36 Patent. Studs are mentioned in Claim 1 as the open sections with the concave lower surface of the plate which provide for contact with the bone. The Plaintiff summarizes this description of studs as being downwardly-descending portions of the lower surface of the plate which [*15] provide the bone contact areas when in use. Claim 5, dependent on Claim 1, adds the additional limitation of the contact elements (studs) being less than 5% of the lower surface of the plates. A term from an independent claim can not be read differently than that term is read in a dependent claim, unless the dependent term also includes further limitations. In this instance, it would be illogical for Synthes to add this further limitation to the definition of studs in Claim 5 if the term already included a 5% or "minimum practicable" limitation (as defined in Claim 1).

The prosecution history also supports Synthes' interpretation of Studs. The patent examiner rejected earlier versions of Synthes' claims based on the Kummer patent. The examiner considered what Kummer calls 'washers and spacers' to be resorbable studs. These "studs" have large, flat areas of contact with the bone, and certainly not the" minimum practicable" area of contact. It seems probable, then, that the examiner understood studs to be a broader term than does DePuy. Therefore, because the claims of the 36 Patent and its prosecution history favor an interpretation more consistent with that offered by Synthes, studs [*16] will be construed as meaning projections that do not mandatorily have the minimum practicable or less than 5% limitation.

c. Definition of Self-Compressing Screw Hole:

Only Claim 4 of the 36 Patent includes a self-compressing screw hole. Defendant argues that this limitation includes only the type of self-compressing screw hole found in U.S. Patent No. Re. *31,628* (Def. Mem., Ex. 4, Re. *31,628* patent) (the *"628* Patent"). This type of screw is defined in the *31,628* patent as a screw hole "formed with a slot which is elongated in the direction of the longitudinal axis of the plate so that the plate will be shifted relatively along this axis when the threaded securing screw is inserted there through and into the bone part". (Def. Mem., Ex. 4, *628* Patent, 1:59-68). Since Claim 4 merely refers to a self-compressing screw hole without further elaboration, the specification must be examined. In the specification of the 36 Patent, Synthes refers to the self-compressing screw hole as the type found in the *628* Patent. During the prosecution of the 36 Patent, the examiner at first rejected the self-compressing screw as "indefinite". (Def. Mem., Ex. 6, Examiner's Response [*17] at 2). In response, Synthes transversed the objection by mentioning that the screw refers to the type disclosed in the disclosure of the *628* Patent. Synthes states clearly that the claim should be read in light of that specification. In other words, Synthes specifically defined a term within one of its claims by adopting a definition found in the *628* Patent's specification. Since a patentee may not proffer an interpretation for the purposes of litigation that would alter the public record, the Court construes self-compressing hole in the manner encouraged by DePuy. See *Southwall Techs, 54 F.3d at 1578.*

On the other hand, it is not clear that Claim 4 must include "one and only one" self compressing hole. Since the claim is unclear, the Court looks to the specification of the 36 Patent. That specification contemplates the use of one or more self compressing screw holes of the type described in Patent No. *31,628.* (36 Patent, 4:13-15). This same specification helps to define the term "self compressing screw hole" and can also be used to determine the number of holes claimed. Reading this specification, the Court concludes that Claim 4 is not limited to just one self [*18] compressing screw hole.

2. **Comparison to the Accused Products:**

In order to grant summary judgment for the Defendant DePuy, the Court must find that no reasonable jury could find that the Accused Products infringe upon Synthes' 36 patent in light of the definition of terms described above. Therefore, we now look to see whether it is beyond dispute that DePuy's products do not infringe on Synthes' 36 Patent.

DePuy argues that it does not infringe any of the asserted claims of the 36 Patent because 1) the features of the undersurface of the accused plates which make reduced, interrupted line contact with the bone, are not the claimed "studs" and 2) the accused plates do not have the screw holes required by the claims. DePuy also argues that Claim 4 is not infringed because the accused plates do not have the self-compressing hole recited in that claim.

a. Studs: Since this term is not limited to projections having "minimum practicable" contact with the bone, a jury could believe that the cut outs between the screw holes in the accused DePuy products are literally, or the substantial equivalent of, the "studs" found in the 36 Patent. Dr. Burstein, DePuy's expert, admits [*19] that the Accused Products make interrupted line contact and that the cut outs between screw holes result in reduced bone contact. The question of infringement here is one for the jury.

b. Screw Holes: Under the broad definition of this term that the Court has accepted, the Court can not conclude beyond doubt that DePuy's Accused Products do not contain this limitation. In fact, DePuy's technical expert admits that under a broad definition of screw hole, DePuy's products would meet the "plurality of screw hole limitation" (although he consistently refers to the openings as 'slots' instead of 'screws') (Pl. Mem., Ex. C, page 161).

c. Self-Compressing Screw Hole: The Court has adopted the narrower definition of the term that DePuy urged. However, even when accepting this definition, Synthes presents significant evidence of infringement under both the literal test and the doctrine of equivalents. Summary determination in DePuy's favor is therefore inappropriate.

3. Anticipation by the Sherman Patent

In order to demonstrate anticipation of the claims that have allegedly been infringed, the alleged infringer must show, by clear and convincing evidence, that each [*20] and every element of a patent claim is disclosed within a single prior art reference. See *Electro Med. Sys., S.A. v. Cooper Life Sciences, Inc., 34 F.3d 1048, 1052 (Fed. Cir. 1994).* DePuy argues that since the Court has adopted the broader definitions of studs and screws that Synthes encouraged, the claims of the 36 Patent that DePuy has allegedly infringed were previously anticipated by U.S. Patent No. *1,105,105* (the "Sherman Patent"). Synthes concedes that there are elements of the 36 Patent that are taught by the Sherman Patent. However, it argues that the following claim limitations are not taught by the Sherman Patent.

1) Studs,

2) open sections/arcuate cut out sections,

3) that the open/arcuate cut out sections be between the screw holes,

4) the requirement that the "intersection of surfaces formed by said cut out sections and the concave lower surfaced of the plate form the studs, and .

5) contact elements less than 5% of the total area of the lower surface of the plate.

(Pl. Mem. at 28). Numbers 1-3 above apply to all asserted claims. If the Court concludes that one of these limitation is not clearly disclosed by the [*21] Sherman Patent, then summary judgment in Defendant's favor based on anticipation would be inappropriate. While DePuy offers some evidence of Synthes' claim limitations being anticipated by the Sherman Patent, this evidence does not qualify as "clear and convincing". Accordingly, summary judgment for DePuy is denied.

4. Summary Judgment for Synthes:

Synthes moves for summary judgment of infringement and validity of Claims 4 and 14 of the 36 Patent. Claim 4 of the 36 Patent if dependent on independent Claim 1. This means that Claim 4 encompasses all the limitations of Claim 1, but also adds a new limitation, specifically the "self-compressing screw hole". The Court has interpreted this limitation from Claim 4 as the "type of screw hole found in the *31,628* Patent". Synthes argument for literal infringement depends on a broader interpretation of the "self compressing screw hole". Synthes infringement claim now depends on the doctrine of equivalents. Since there are definitely factual disputes concerning infringement of this claim, summary judgment will be denied.

Claim 14 involves two new disputed claim limitations; arcuate-cut out sections and the intersection of surfaces formed [*22] by said cut out sections ands the concave lower surface of the plate. Synthes interprets "arcuate cut out sections" as features on the lower surface of the plate "resulting from arched concavities shaped into that lower surface and that the surfaces must cross or pass through one another". Assuming the Court were to adopt these requested constructions, summary judgment could not be granted. DePuy presents evidence that Synthes claims have been anticipated and/or were obvious in light of the prior art. To determine anticipation and obviousness are fact-intensive inquiries that are currently subject to dispute. Therefore, the Court denies summary judgment to Synthes.

IV. CONCLUSION

To summarize, the Court denies summary judgment to both parties. It has accepted broad definitions of "studs" and "screw holes" and a narrow definition of self-compressing screw hole in its denial of summary judgment to Defendant DePuy. However, there are factual disputes as to the question of infringement by DePuy and summary judgment is likewise denied to Synthes.

An appropriate order follows.

ORDER

AND NOW, this 29th day of November, 1999, upon consideration of Defendant's Motion [*23] for Summary Judgment as to Non-infringement and Invalidity (Docket No. 18), Plaintiffs' Response thereto (Docket No. 24), as well as Plaintiffs' Motion for Summary Judgment as to Infringement and Validity of Claims 4 and 14 (Docket No. 20) and Defendant's Response thereto (Docket No. 25); it is hereby **ORDERED** that both Motions are **DENIED.**

BY THE COURT:

RONALD L. BUCKWALTER, J.

LEXSEE 51 USPQ 2D 1764

SPORT SQUEEZE, INC., Plaintiff, vs. PRO-INNOVATIVE CONCEPTS, INC. et al., Defendants.

CASE NO. 97-CV-115 TW (JFS)

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF CALIFORNIA

1999 U.S. Dist. LEXIS 16681; 51 U.S.P.Q.2D (BNA) 1764

March 31, 1999, Decided

April 1, 1999, Filed

CASE SUMMARY

PROCEDURAL POSTURE: The court construed the disputed claim language in plaintiff's suit against defendant for patent infringement.

OVERVIEW: Plaintiff sued defendant for patent infringement involving a hand-held exercise ball. Defendant was the purported inventor and owner of three patents related to the exercise balls. The invention was a core of tightly-packed dry particles surrounded by layers of latex balloons. The court held a claim construction hearing to determine the meaning of the word particles. The court considered the disputed claims language and the meaning of the term particles, as a matter of law. The three patents contained a wide spectrum of language regarding particles, describing them in narrow and in broad terms. In all three patents, when defendant sought to limit the particles in its claims to a particular size or shape, it qualified the term by including the size or shape limitation. The court concluded that the term particles in the second and third patents meant particles in its ordinary sense without limitation based on the size of shape of millet. Specifically, the court found that the term particles contemplated small specks of matter, including but not limited to, starch particles, microsphere particles, hard plastic or silicon beads and millet.

OUTCOME: The court issued an order resolving only the issue of claim construction finding that the term particles in the claims of two patents meant particles in the ordinary sense without limitation on size or shape of millet; however, the court expressed no opinion on the determination of infringement.

CORE CONCEPTS

Patent Law : Infringement : Claim Interpretation
Construing a claim to determine its scope and meaning, also known as claim construction, is a pure question of law for the court. The language of the claim defines the scope of the protected invention. Words in a patent claim are construed as they would be understood by a reader skilled in the relevant art unless it appears that the inventor used the words differently.

Patent Law : Infringement : Claim Interpretation
When interpreting disputed claim language, the court must first look to intrinsic evidence, including the patent itself, including the claims, the specification and, if in evidence, the prosecution history.

Patent Law : Infringement : Claim Interpretation
There is presumed to be a difference in meaning and scope when different words or phrases are used in separate patent claims. To the extent that the absence of such a difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between claims is significant. The doctrine of claim differentiation has its greatest force when an interpretation of a dependent and independent claim would render the dependent claim superfluous. The doctrine may also be used to interpret an independent claim in light of another independent claim.

Patent Law : Infringement : Claim Interpretation

Although the doctrine of claim differentiation may at times be controlling, construction of claims is not based solely upon the language of other claims; the doctrine cannot alter a definition that is otherwise clear from the claim language, description, and prosecution history.

Patent Law : Infringement : Claim Interpretation
While the specification may aid the court in interpreting the meaning of disputed claim language, particular embodiments and examples appearing in the specification will not generally be read into the claims.

Civil Procedure : Preclusion & Effect of Judgments : Law of the Case Doctrine
The law of the case doctrine merely expresses the practice of a court generally to refuse to reopen what has been decided. It is not a limit to the court's power. The court retains inherent authority to revise interim or interlocutory orders any time before judgment, including orders denying motions for summary judgment. Fed. R. Civ. P. 54(b).

COUNSEL:
[*1] For SPORT SQUEEZE, INC., plaintiff: Jeffrey R Smith, Smith and Brown, San Diego, CA.

For PRO-INNOVATIVE CONCEPTS, INC., MARK A SCATTERDAY, defendants: Steven J Nataupsky, Knobbe Martens Olson and Bear, Newport Beach, CA.

For PRO-INNOVATIVE CONCEPTS, INC., MARK A SCATTERDAY, defendants: Albert L Schmeiser, Mesa, AZ.

For PRO-INNOVATIVE CONCEPTS, INC., MARK A SCATTERDAY, counter-claimants: Steven J Nataupsky, Knobbe Martens Olson and Bear, Newport Beach, CA.

For SPORT SQUEEZE, INC., counter-claimant: Jeffrey R Smith, Smith and Brown, San Diego, CA.

JUDGES:
Judge THOMAS J. WHELAN, United States District Court, Southern District of California.

OPINIONBY:
THOMAS J. WHELAN

OPINION:

ORDER RE: CLAIM CONSTRUCTION

I. Introduction

In accordance with the Federal Circuit's ruling in *Markman v. Westview Instruments, 52 F.3d 967, 970-71 (Fed. Cir. 1995)* (en banc), aff'd *517 U.S. 370, 116 S. Ct. 1384, 134 L. Ed. 2d 577 (1996),* a claim construction hearing was held on March 5, 1999. Stephen Beuerle, Robert Laurenson and John Benassi appeared for plaintiff Sport Squeeze, Inc. Steven Nataupsky, Ann Byun and Darrell Olson appeared for defendants Pro-Innovative [*2] Concepts, Inc. and Mark Scatterday.

The court has considered the three patents at issue in this case, the specifications and file histories of the three patents, all briefs submitted by the parties including supporting declarations and oral arguments made at the hearing, which are incorporated herein by reference. By this order, the court construes the disputed claim language as a matter of law.

II. Background

This is a patent infringement lawsuit involving a deformable hand-held exercise ball. Defendant Mark Scatterday is the purported inventor and owner of three patents related to exercise balls which are squeezed in the hand to relieve stress and exercise the limbs. The invention consists of a core of tightly packed dry particles surrounded by layers of resilient latex balloons, enabling the ball to be squeezed into deformable shapes. Scatterday's company Pro-Innovative Concepts, Inc. ("Pro-Innovative") manufactures and sells an exercise ball called "The Gripp(R)" which embodies one of the ways the invention may be implemented.

Scatterday owns three United States Patents on the exercise grip. The first patent, U.S. Patent number *5,190,504* ("the *'504* Patent"), was issued [*3] to Scatterday on March 2, 1993. The second patent, U.S. Patent number *5,350,342* ("the *'342* Patent") was a continuation patent from the *'504* Patent issued to Scatterday on September 27, 1994. The third patent, U.S. Patent number *5,556,358* ("the *'358* Patent") was a continuation patent to the *'342* Patent and was issued on September 17, 1996.

Pro-Innovative alleges that plaintiff Sport Squeeze International ("Sport-Squeeze") manufactured and sold its own squeeze ball under the brand name "Ad Squeeze." Pro-Innovative contends that the Ad Squeeze ball infringes Claims 1, 4-6 and 8 of the *'342* Patent and Claims 1-4 of the *'358* Patent. n1

n1 As the parties noted in their briefs, the court has received commercial samples of both THE GRIPP(R) and the Ad Squeeze products produced by the parties. The court is aware that the construction of the claims in a patent does not depend on how those patents were commercially implemented. See, e.g., *Zenith Lab. v. Bristol-Myers Squibb Co., 19 F.3d 1418, 1423 (Fed. Cir.*

1994); International Visual Corp. v. Crown Metal Mfg. Co., 991 F.2d 768, 771-72 (Fed. Cir. 1988). The commercial samples furnished by both Sport-Squeeze and Pro-Innovative played no part in the court's consideration of the arguments of the parties or the court's determination of how the disputed patent language should be construed.

[*4]

III. "Particles"

For the claim construction hearing, Claims 2-4 of the *'358* Patent were at issue. The parties agree that the only claim term that is in dispute is the word "particles" as it appears in independent Claim 2. n2 Thus, the purpose of the Markman hearing was to determine the meaning of the word "particles." Independent Claim 2 of the *'358* Patent, in its entirety, reads as follows: (See Column 6, Lines 5-20).

n2 The term "particles" is also found in Claims 1 and 8 of the *'342* Patent and Claim 1 of the *'358* Patent.

2. A semi-resilient exercise grip comprising:

a core containing a deformable mixture of tightly packed individual dry particles that are in continuous contact with each other; and

a resilient covering surrounding said core, wherein said covering is in the form of a plurality of nested sacks, wherein each sack is made of a resilient material and includes an opening, and wherein the sacks are located about the core, the openings of adjacent sacks are spaced [*5] apart from each other, and wherein each sack applies its own inward force on the core and the total inward force on the core is the combined total of the individual inward forces exerted on the core by each of the sacks making up the covering.

Claims 3 and 4 of the *'358* Patent further limit the coverings of the exercise grip. Dependent Claims 2 and 3, in their entirety, read as follows: (See Column 6, Lines 21-25).

3. The grip of claim 2 wherein each of the sacks that make up the covering are substantially ball-shaped when in a non-stressed state.

4. The grip of claim 2 wherein each of the sacks are made of a latex rubber material.

Sport Squeeze contends that the term "particles" is limited to particles that are similar in size and shape to millet (roughly the size of bird seed), which is one of the examples of particles disclosed in the Scatterday patents. The allegedly infringing Ad Squeeze product uses silicon beads which are much smaller in size than millet. Accordingly, Sport-Squeeze contends that the term "particles" is limited to larger, millet-sized particles, which, under its proffered construction, would result in the Ad Squeeze product [*6] not infringing the asserted claims.

In opposition, Pro-Innovative contends that the term "particles" should be given its broad and ordinary meaning which includes particles not limited in size and shape to millet. Specifically, Pro-Innovative requests the court to construe the term "particles" to mean "small specks of matter which include starch particles, microsphere particles, hard plastic or silicon beads and millet."

IV. Discussion

A. Legal Standards

a. Construing the Term "Particles" in the *'342* and *'358* Patents is a Question of Law for the Court

Construing a claim to determine its scope and meaning, also known as "claim construction," is a pure question of law for the court. *Markman, 52 F.3d 967, 970-71.* The language of the claim defines the scope of the protected invention. *Bell Communications Research v. Vitalink Communications Corp., 55 F.3d 615, 619-620 (Fed. Cir. 1995).* "Words in a patent claim are construed as they would be understood by a reader skilled in the relevant art unless it appears that the inventor used the words differently." *Cole v. Kimberly-Clark Corp., 102 F.3d 524, 531 (Fed. Cir. 1997).* [*7]

When interpreting disputed claim language, the court must first look to "intrinsic" evidence, including "the patent itself, including the claims, the specification and, if in evidence, the prosecution history." *Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996)* (citing *Markman, 52 F.3d at 979).* The parties agree that the disputed claim language can be construed with reference to intrinsic evidence only. Thus, it would be improper to look to extrinsic evidence. Id. at 1583.

b. The Doctrine of "Claim Differentiation"

"There is presumed to be a difference in meaning and scope when different words or phrases are used in separate [patent] claims. To the extent that the absence of such [a] difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between claims is significant." *Tandon Corp. v. U.S. Int'l Trade Comm'n,*

831 F.2d 1017, 1023 (Fed. Cir. 1987). The doctrine of claim differentiation has its greatest force when an interpretation of a dependent and independent claim would render the dependent claim superfluous. [*8] *Beachcombers v. WildeWood Creative Products, Inc., 31 F.3d 1154, 1162 (Fed. Cir. 1994)* (interpretation that renders dependent claim superfluous is "presumptively unreasonable" under doctrine of claim differentiation); *United States v. Telectronics, Inc., 857 F.2d 778, 783 (Fed. Cir. 1988)* (where some claims are broad and others narrow, the narrow claim limitations cannot be read into the broad claims). The doctrine may also be used to interpret an independent claim in light of another independent claim. See, e.g., *Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1055 (Fed. Cir. 1988); Caterpillar Tractor Co. v. Berco, SPA, 714 F.2d 1110, 1116 (Fed. Cir. 1983).*

"Although the doctrine of claim differentiation may at times be controlling, construction of claims is not based solely upon the language of other claims; the doctrine cannot alter a definition that is otherwise clear from the claim language, description, and prosecution history." *O.I. Corp. v. Tekmar Co., Inc., 115 F.3d 1576, 1582 (Fed. Cir. 1997);* see also *Comark Communications, Inc. v. Harris Corp., 156 F.3d 1182, 1187 (Fed. Cir. 1998)* [*9] ("While we recognize that the doctrine of claim differentiation is not a hard and fast rule of construction, it does create a presumption that each claim in a patent has a different scope.").

B. Claim Differentiation Supports Pro-Innovative's Construction

Pro-Innovative argues that its three exercise grip patents contain a wide spectrum of language regarding certain "particles," describing them in narrow and broad terms. It argues that the claims of the *'342* Patent use the term "particles" both with and without qualifying language, and that the *'358* Patent includes no language limiting "particles" based on size and shape. Upon review of the three patents, the court finds that the doctrine of claim differentiation supports Pro-Innovative's position.

1. The *'504* Patent

Claim 1 of the first patent issued to Scatterday, the *'504* Patent issued in 1993, limited the "particles" used to fill the exercise ball to millet-sized particles. (See Column 5, Lines 23-26).

1. A semi-resilient exercise grip comprising a nonresilient core containing a deformable mixture of individual particles identical in size and shape to millet

Claim 7 of the *'504* Patent is also [*10] limited to "millet-sized" particles. (See Column 6, Lines 15-19). The parties do not dispute that the plain language of Claim 1 of the *'504* Patent and the patent's prosecution history confirm that Claim 1 is limited to millet-sized particles.

2. The *'342* Patent

However, the term "particles" in the subsequently issued *'342* Patent is not expressly limited to "millet-sized" particles. Specifically, Claims 1-3 of the *'342* Patent read: (See Column 5, Lines 27-43; Column 6, Line 1).

1. A semi resilient exercise grip comprising a non-resilient dry core containing a deformable mixture of tightly packed individual particles that are in continuous contact with each other.

2. The grip of claim 1 wherein the particles are hard and are similar in size and shape to millet.

3. The grip of claim 2 wherein the particles are millet.

Applying the doctrine of claim differentiation, the term "particles" in Claim 1 cannot be limited to particles "similar in size and shape to millet." Under such a construction, Claim 2 would have the same scope as Claim 1, rendering Claim 2 superfluous--a construction that is "presumptively unreasonable. [*11] " *Beachcombers, 31 F.3d at 1162.* Sport Squeeze presented no evidence during the hearing or in its papers rebutting the strong presumption that the "millet-sized" limitations in dependent Claim 2 should not be incorporated into Claim 1.

Sport Squeeze argues that the prosecution history of the *'342* Patent supports a narrow reading of the term "particles." Specifically, Sport Squeeze emphasizes that the Patent Office rejected the initial Claim 7 as obvious under U.S. Patent No. *3,601,923* issued to Rosenberg. (See Sport Squeeze Exhibit G). n3 To overcome the Patent Office's rejection, Scatterday limited the "particles" in initial Claim 7 to "substantially millet-sized" particles and explained to the Patent Examiner that the "millet-sized" particles in the revised claim distinguished the claim from Rosenberg, which used considerably smaller starch particles. (See Sport Squeeze Exhibit B, at 6-7 (Stamp no. 122-123) (stating that "the tiny particles used by Rosenberg form a crucial component of his invention.")). n4

n3 The claim which became Claim 7 of the *'342* Patent was originally designated as Claim 15 in Scatterday's earlier applications. For purposes of this Order, the court will refer to Claim 15 as

the "initial Claim 7," and the claim issued by the patent office as "issued Claim 7." [*12]

n4 The Patent Office also rejected various claims of the *'342* Patent under the doctrine of "double-patenting." Scatterday subsequently filed a terminal disclaimer to cure the rejection so that all three patents (*'504*, *'342*, and *'358*) would expire on the date of the first patent. See *In re Goodman, 11 F.3d 1046, 1052 (Fed. Cir. 1993)* (filing of terminal disclaimer cures double patenting rejection).

In essence, Sport-Squeeze argues that the prosecution history of Claim 7 (which resulted in a claim dependent upon "millet-sized" particles) supports its contention that the "millet-sized" limitation should be implied into claims that do not contain this limitation. This argument is unpersuasive. The fact that Scatterday limited "particles" in initial Claim 7 to "millet-sized" particles while leaving "particles" in Claim 1 without such a limitation supports Pro-Innovative's contention that the term "particles," standing alone, is not limited to particles that are millet-sized. Moreover, the difference between the "particles" in Claim 1 and issued Claim 7 provides additional support [*13] for Pro-Innovative's arguments that claim differentiation forecloses a construction of the term "particles" limited to particles that are millet-sized. n5

n5 Sport-Squeeze argues that Scatterday represented to the Patent Office during prosecution of the *'342* Patent that millet-sized particles were essential to the semi-resilient nature of the exercise grip. (See Sport-Squeeze's Opening Brief at 9-10 (quoting Sport-Squeeze's Exhibit I, at 6)). However, those comments were made in reference to a claim which *explicitly* contained a "millet-sized" limitation. Thus, Sport-Squeeze's "file wrapper estoppel" arguments concerning the other claims are without merit as this explanation was not offered to obtain allowance on any other claim. Moreover, Sport-Squeeze presented no evidence during the Markman hearing that the invention's semi-resilient characteristics depend upon millet-sized particles. In any event, this statement does not overcome the presumption raised by the doctrine of claim differentiation.

[*14]

3. The *'358* Patent

Approximately two years after the *'342* Patent was issued, the Patent Office awarded Scatterday the *'358* Patent, the primary patent at issue here. Significantly, unlike the *'504* and *'342* Patents, the term "millet" does not appear in any of the issued claims of the *'358* Patent. The sole mention of "millet" appears in the specification: (See Column 3, Lines 10-15):

In practice, seeds such as millet have been used as the particles. As an alternative, the particulate [sic] material can be hard plastic or silicon beads or any other matter that is similar in size and shape to millet and that is hard enough to withstand the compressive pressures experienced when the grip is being squeezed by a user.

Sport-Squeeze argues that this language discloses that the "particles" in the *'358* Patent are limited to millet-sized particles. However, while "the specification may aid the court in interpreting the meaning of disputed claim language, particular embodiments and examples appearing in the specification will not generally be read into the claims." *Comark Communications, Inc., 156 F.3d 1182 at 1187;* see also *Laitram Corp. v. Cambridge Wire Cloth Co., 863 F.2d 855, 865 (Fed. Cir. 1988)* [*15] ("References to a preferred embodiment, such as those often present in a specification, are not claim limitations."). Sport-Squeeze has provided no basis for reading the specification's illustrative use of "millet-sized" into the claims of the patent. The court has found nothing in the long and somewhat confusing prosecution history of the *'358* Patent which would warrant a narrow reading of "particles" inconsistent with its plain meaning and the construction of that term in the *'342* Patent.

With all three patents, when Pro-Innovative sought to limit the "particles" in its claims to a particular size or shape, it qualified that term by including the limitation that the particles be the size or shape of "millet." When Pro-Innovative did not wish to limit the size or shape of the "particles," it did not include any size or shape limitation.

i. Application of Claim Differentiation to the *'358* Patent

Sport-Squeeze contends that the doctrine of claim differentiation cannot be applied to the *'358* Patent because the doctrine is "inapplicable to continuation patents." The sole case Sport Squeeze relies upon, *Jonsson v. Stanley Works, 903 F.2d 812 (Fed. Cir. 1990),* [*16] held that the prosecution history of one patent can be used to determine the scope and to interpret the meaning of another patent where both patents stem from a common parent application. *903 F.2d at 818.* The court found it unnecessary to apply the doctrine of claim differentiation because the court's finding that the claim

contained a limitation existing in a separate dependent claim was supported by the prosecution history, the patent, the specifications, and deposition testimony. *Id. at 820* ("Hence, since it is apparent that the court had ample evidence to determine the scope of the '912 patent, Jonsson's reliance on claim differentiation requires no discussion."). Thus, Jonsson merely reinforces the rule that the doctrine of claim differentiation can be overcome by a patent's prosecution history. n6

n6 Most of the sections of Jonsson quoted in Sport-Squeeze's Opening Brief were not the opinion of the court, but rather arguments asserted by the parties.

In this case, however, [*17] the court need not necessarily rely upon the doctrine of claim differentiation to conclude that the "particles" in the *'358* Patent are not limited to "millet-sized" particles. As discussed in the preceding section of this order, nothing in the prosecution history or specifications justifies departing from the plain meaning of the term "particles." Rather, the prosecution history of all three patents reveals that both Scatterday and the patent examiner understood that differing particle sizes were significant in light of Tarnoff and Rosenberg.

Although not necessary to the court's conclusion, it notes that the doctrine of claim construction may provide additional support for Pro-Innovative's position. All three patents (1) involved the deformable exercise grip, (2) were issued over a relatively short period (three years), (3) involved the same patent examiner (Stephen Crow), and (4) made reference to the same prior art references. These facts support the court's conclusion that the term "particles" in the *'358* Patent should be construed consistently with that term in the *'342* Patent.

V. Sport-Squeeze's Arguments in Opposition

Sport-Squeeze presents two main arguments to [*18] support its contrary position that the "particles" in the *'358* Patent must be millet-sized. First, Sport-Squeeze argues that the term "particles" should be narrowly construed to avoid conflict with prior art patents. Second, Sport-Squeeze argues that Judge Moskowitz previously ruled that the "particles" in the *'342* and *'358* Patents are millet-sized and that this determination is "law of the case."

a. Sport-Squeeze's Argument that a Narrow Reading of "Particles" is Necessary to Avoid Invalidation in light of Tarnoff is Logically Flawed

Sport-Squeeze argues that a broad construction of "particles" should be avoided because such a construction would read back on the Tarnoff prior art. According to Sport-Squeeze, a broad reading of the term "particles" would render the *'342* and *'358* Patents invalid under Tarnoff and Rosenberg because both of these patents use microspheres that are substantially smaller than millet.

Sport-Squeeze's argument is logically flawed because it assumes the term "particles" must be analyzed as an isolated term, construed outside the context of the claim it limits. In fact, it is of little consequence that a *single term* in a patent claim reads back [*19] on a term in a prior art patent so long as the claim *as a whole* does not read back on a claim in the prior art. Here, particle size is only one of many possible limitations contained in the claims of the *'342* and *'358* Patents. (See, e.g., Pro-Innovative's Exhibit 369). Claim 2 of the *'358* Patent, for example, contains numerous limitations not found in Tarnoff or Rosenberg, including: (1) a plurality of nested sacks, (2) openings of adjacent sacks that are spaced far apart from one another, (3) each sack applies inward force on the core, and (4) the total inward force is the combined total of the individual inward forces. Id. These limitations, rather than an implied limitation on particle size, likely formed the basis for patentability of Claim 2. n7

n7 In its Reply brief, Sport-Squeeze contends that "to have any differentiation between the claimed squeeze ball and the prior art, the term 'particle' must be defined as including particles approximately millet-like, but excluding microspheres ranging from 0.0001 inches to 0.06 inches." (See Sport Squeeze's Reply at 6:17-19). A similar argument appears in its Opening brief, where Sport-Squeeze argues that a narrow reading of the term "particle" is necessary to avoid conflict with Tarnoff. (See Sport-Squeeze's Opening Brief at 5:11-15). This arguments are rejected for the reasons stated in the text.

[*20]

Thus, the court rejects Sport-Squeeze's argument that the term "particles" must be construed narrowly because the term may read back on the microspheres of Tarnoff. Moreover, Sport-Squeeze made no arguments during the Markman hearing or in its briefs that the broad construction of "particle" urged by Pro-Innovative would cause any of the *claims* of the *'342* or *'358* Patents to read back on Nichols, Rosenberg, Cherk, or Tarnoff.

b. Judge Moskowitz's Previous Ruling is not "Law of the Case"

Sport-Squeeze relies heavily upon the language of two orders from Judge Moskowitz, both dated August 10, 1998. (See Sport-Squeeze Exh. D, E). Sport-Squeeze relies particularly on page 5 of Judge Moskowitz's August 10, 1998 order denying Pro-Innovative's motion for summary judgment. (See Order Denying Motion for Summary Judgment on Patent Infringement (Doc # 106)). In that order, Judge Moskowitz rejected Pro-Innovative's contention that the term "particles" in the *'358* Patent consisted of particles of any shape and size. He noted that this construction was "incredibly broad" and "unsupported by the record." (See id. at 5:15-23). Sport-Squeeze contends that Judge Moskowitz's [*21] ruling is "law of the case" and is binding on this court. The court finds this argument unpersuasive for two reasons.

First, the sole issue before Judge Moskowitz was whether Pro-Innovative was entitled to summary judgment on the issue of Sport-Squeeze's alleged infringement of the *'358* patent. Since a Markman hearing had not been conducted, the question of claim construction was not before the court. In fact, in a footnote Judge Moskowitz observed that the parties had failed to lodge the Rosenberg and Tarnoff patents, and that without those references, "the Court cannot at this time determine whether 'particles' should be construed to include the 'size and shape of millet' limitation urged." (See id. at 6 n.2). n8 At the conclusion of his order, Judge Moskowitz scheduled a Markman hearing and set a briefing schedule, negating any inference that he intended his previous order to serve as the final word on the construction of the three Scatterday patents.

n8 Judge Moskowitz's order adopted Sport-Squeeze's argument that the term "particles" must be narrowly construed to avoid reading back on the particle-size aspect of the Tarnoff prior art. (See Part IV.a, *supra*). This conclusion was understandable since Judge Moskowitz did not have the Tarnoff prior art available to him at the time of the ruling.

[*22]

Second, the court notes that, to the extent "law of the case" is applicable, it "merely expresses the practice of [a] court[] generally to refuse to reopen what has been decided." *Christianson v. Colt Industries Operating Corp., 486 U.S. 800, 817, 100 L. Ed. 2d 811, 108 S. Ct. 2166 (1988)* (quoting *Messenger v. Anderson, 225 U.S. 436, 444, 56 L. Ed. 1152, 32 S. Ct. 739 (1912))* (Holmes, J.). It is not a limit to the court's power. Id.; *Capital Investors Co. v. Executors of Morrison's Estate, 584 F.2d 652, 654 (4th Cir. 1978)* ("The principle [of law of the case] is not absolute nor inflexible."). The court retains inherent authority to revise interim or interlocutory orders any time before judgment, including orders denying motions for summary judgment. See, e.g., FED. R. CIV. P. 54(b) (any order not certified under Rule 54(b) and which adjudicates fewer than all the claims as to all the parties "is subject to revision at any time before the entry of [final] judgment"); *Balla v. Idaho State Bd. of Corrections, 869 F.2d 461, 465 (9th Cir. 1989)* ("Courts have inherent power to modify their interlocutory orders [*23] before entering a final judgment."); *Curran v. Kwon, 153 F.3d 481, 487 (7th Cir. 1998)* ("When a district judge is presented with additional evidence, therefore, he is free to revisit a denial of summary judgment."). Thus, even assuming the issue of claim construction was addressed in the court's August 10, 1998 Order, the doctrine of "law of the case" would not preclude this court from revisiting the issue, especially where, as here, the parties presented evidence and argument they did not present at the time the court issued its previous order.

VI. Conclusion

For the foregoing reasons, the court concludes that the term "particles" in the claims of United States Patent Nos. *5,350,342* and *5,556,358* means particles in its ordinary sense without limitation based on the size or shape of millet. Specifically, the court finds that the term "particles" contemplates small specks of matter, including but not limited to, starch particles, microsphere particles, hard plastic or silicon beads and millet. n9

n9 This order resolves only the issue of claim construction. The court expresses no opinion on the determination of infringement, the applicability of any defenses Sport-Squeeze may wish to assert, or the viability of the non-patent claims.

[*24]

Finally, the motion cut-off date in this matter is continued until **June 14, 1999**. n10

n10 The parties may contact the court to obtain hearing dates for subsequent motions. The court notes that it may need to reset the pretrial conference date set for June 1, 1999 if additional motions are filed.

IT IS SO ORDERED.

Dated: March 31, 1999

Judge THOMAS J. WHELAN

United States District Court

Southern District of California

01 JUN -4 PM 3:10

DEPUTY

ORIGINAL

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99cv2668 H (AJB)

STIPULATION AND ~~[PROPOSED]~~ ORDER PERMITTING GEN-PROBE INCORPORATED TO FILE REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN EXCESS OF TEN (10) PAGES IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept: Courtroom 1

I. FACTS

1. Whereas, Plaintiff Gen-Probe Incorporated has filed a Motion for Partial Summary Judgment, which is set to be heard by this Court on June 8, 2001 at 10:30 a.m.

2. Whereas, due to the nature and number of issues to be addressed in its Reply Memorandum of Points Authorities, Gen-Probe believes in good faith that it is necessary for it to exceed the ten (10) page limitation set forth in Local Rule 7.1(h) in order to adequately brief the myriad of issues for this Court and seeks leave of Court to do so;

3. Whereas, counsel for the parties have met and conferred and Defendant Vysis, Inc. has no objection to Gen-Probe filing a reply memorandum in excess of ten (10) pages, but not to

exceed fifteen (15) pages.

II. STIPULATION

The parties, through their respective counsel, stipulate that Gen-Probe shall be entitled to file and serve a Reply Memorandum of Points and Authorities in Support of its Motion for Partial Summary Judgment that is in excess of ten (10) pages, but not to exceed fifteen (15) pages in length.

Dated: May 30, 2001

STEPHEN P. SWINTON
J. CHRISTOPHER JACZKO
COOLEY GODWARD LLP

R. WILLIAM BOWEN, JR.
GEN-PROBE INCORPORATED

By: _____
J. Christopher Jaczko

Attorneys for Plaintiff
GEN-PROBE INCORPORATED

Dated: May ____, 2001

CHARLES E. LIPSEY (*pro hac vice*)
THOMAS W. BANKS (195006)
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
THOMAS W. BANKS (195006)

By: _____
Thomas W. Banks

Attorneys for Defendant
VYSIS, INC.

[PROPOSED] ORDER

IT IS SO ORDERED

Dated: 6/1/01

_____
JUDGE OF THE DISTRICT COURT

exceed fifteen (15) pages.

II. STIPULATION

The parties, through their respective counsel, stipulate that Gen-Probe shall be entitled to file and serve a Reply Memorandum of Points and Authorities in Support of its Motion for Partial Summary Judgment that is in excess of ten (10) pages, but not to exceed fifteen (15) pages in length.

Dated: May 30, 2001

STEPHEN P. SWINTON
J. CHRISTOPHER JACZKO
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R. WILLIAM BOWEN, JR.
GEN-PROBE INCORPORATED

By: _____
J. Christopher Jaczko

Attorneys for Plaintiff
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Dated: May 30, 2001

CHARLES E. LIPSEY (*pro hac vice*)
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THOMAS W. BANKS (195006)

By: _____
Thomas W. Banks

Attorneys for Defendant
VYSIS, INC.

[PROPOSED] ORDER

IT IS SO ORDERED

Dated: _____

_____
JUDGE OF THE DISTRICT COURT

PROOF OF SERVICE
(FRCP 5)

I am a citizen of the United States and a resident of the State of California. I am employed in San Diego, State of California, in the office of a member of the bar of this Court, at whose direction the service was made. I am over the age of eighteen years, and not a party to the within action. My business address is 4365 Executive Drive, Suite 1100, San Diego, California 92121-2128. On the date set forth below I served the documents described below in the manner described below:

1. **STIPULATION AND [PROPOSED] ORDER PERMITTING GEN-PROBE INCORPORATED TO FILE REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN EXCESS OF TEN (10) PAGES IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT**

☐ (BY U.S. MAIL) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of correspondence for mailing with the United States Postal Service, and I caused such envelope(s) with postage thereon fully prepaid to be placed in the United States Postal Service at Palo Alto, California.

☐ (BY MESSENGER SERVICE) by consigning the document(s) to an authorized courier and/or process server for hand delivery on this date. See attached Proof of Personal Service.

☐ (BY FACSIMILE) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of document(s) to be transmitted by facsimile and I caused such document(s) on this date to be transmitted by facsimile to the offices of addressee(s) at the numbers listed below.

☑ (BY OVERNIGHT MAIL) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of correspondence for overnight delivery, and I caused such document(s) described herein to be deposited for delivery to a facility regularly maintained by Federal Express for overnight delivery.

on the following part(ies) in this action:

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Executed on May 30, 2001, at San Diego, California.

Liz Hoke

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Attorneys for Plaintiff
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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC., Defendant.	No. 99cv2668 H (AJB) HON. MARILYN L. HUFF **STIPULATION AND [PROPOSED] ORDER ALLOWING GEN-PROBE INCORPORATED TO FILE UNDER SEAL CERTAIN DOCUMENTS UPON WHICH IT RELIES TO SUPPORT ITS REPLY RE MOTION FOR PARTIAL SUMMARY JUDGMENT** Date: June 8, 2001 Time: 10:30 a.m. Dept.: Courtroom 1

I. FACTS

1. On September 18, 2000, this Court entered a Protective Order to govern the use and disclosure of confidential information disclosed in discovery in this litigation, a true and correct copy of that Protective Order and the subsequent amendment thereto are attached hereto as Exhibit A. Pursuant to paragraph 13 of the Protective Order, no documents shall be filed under seal unless

the Court issues a separate Order upon application of the affected party.

2. Gen-Probe Incorporated ("Gen-Probe") has moved for partial summary judgment and in support of its reply papers will lodge documents and testimony that have been designated by Vysis as confidential, including its Reply Memorandum.

3. As Exhibit 13 in support of its Motion for Partial Summary Judgment, Gen-Probe relies upon excerpts from the transcript of the deposition of Anthony J. Janiuk, taken May 16, 2001. Pursuant to the Protective Order, the deposition transcript is Confidential-Attorneys Only.

4. As Exhibit 14 in support of its Motion for Partial Summary Judgment, Gen-Probe relies upon excerpts from the transcript of the deposition of David Ward, Ph.D., taken May 18, 2001. Pursuant to the Protective Order, the deposition transcript is Confidential-Attorneys Only.

5. As Exhibit 16 in support of its Motion for Partial Summary Judgment, Gen-Probe relies upon excerpts from the transcript of the deposition of Jon Laurie, Ph.D., taken February 15, 2001. Pursuant to the Protective Order, the deposition transcript is Confidential-Attorneys Only.

6. As Exhibit 17 in support of its Motion for Partial Summary Judgment, Gen-Probe relies upon excerpts from the transcript of the deposition of Walter King, Ph.D., taken April 18, 2001. Pursuant to the Protective Order, the deposition transcript is Confidential-Attorneys Only.

7. As Exhibit 18 in support of its Motion for Partial Summary Judgment, Gen-Probe relies upon excerpts from the transcript of the deposition of Donald Neil Halbert, Ph.D., taken April 19, 2001. Pursuant to the Protective Order, the deposition transcript is Confidential-Attorneys Only.

8. The relevant portions of the forgoing exhibits are contained in the sealed envelope attached hereto as Exhibit "B" and are marked as Exhibits 13-18, respectively. The Reply Memorandum is contained in the envelope marked as Exhibit "C".

II. STIPULATION

The parties, through their respective counsel, stipulate that the portions of Anthony Janiuk, David Ward, Ph.D., Jon Lawrie, Ph.D., Walter King, Ph.D., and Donald Neil Halbert, Ph.D. deposition transcripts upon which Gen-Probe relies to support its Motion for Partial Summary

///

Judgment shall be filed under seal in accord with the terms of the Protective Order entered in this case.

Dated: June 1, 2001

STEPHEN P. SWINTON
J. CHRISTOPHER JACZKO
COOLEY GODWARD LLP

DOUGLAS E. OLSON
BROBECK PHLEGER & HARRISON LLP

R. WILLIAM BOWEN, JR.
GEN-PROBE INCORPORATED

By: _____
J. Christopher Jaczko

Attorneys for Plaintiff
Gen-Probe Incorporated

Dated: June 1, 2001

CHARLES E. LIPSEY (*pro hac vice*)
THOMAS W. BANKS (195006)
FINNEGAN,HENDERSON,FARABOW,
GARRETT & DUNNER, LLP
THOMAS W. BANKS (195006)

By: _____
Thomas W. Banks

Attorneys for Defendant
Vysis, Inc.

IT IS SO ORDERED

Gen-Probe may file the excerpts of the deposition transcripts of Anthony Janiuk, David Ward, Ph.D., Jon Lawrie, Ph.D., Walter King, Ph.D., and Donald Neil Halbert, Ph.D., upon which its relies to support its Motion for Partial Summary Judgment in accord with the terms of the Protective Order entered in this case.

Dated:_____

_____
JUDGE OF THE DISTRICT COURT

Judgment shall be filed under seal in accord with the terms of the Protective Order entered in this case.

Dated: June 1, 2001

STEPHEN P. SWINTON
J. CHRISTOPHER JACZKO
COOLEY GODWARD LLP

DOUGLAS E. OLSON
BROBECK PHLEGER & HARRISON LLP

R. WILLIAM BOWEN, JR.
GEN-PROBE INCORPORATED

By: _____
J. Christopher Jaczko

Attorneys for Plaintiff
Gen-Probe Incorporated

Dated: June 1, 2001

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THOMAS W. BANKS (195006)
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THOMAS W. BANKS (195006)

By: _____
Thomas W. Banks

Attorneys for Defendant
Vysis, Inc.

IT IS SO ORDERED

Gen-Probe may file the excerpts of the deposition transcripts of Anthony Janiuk, David Ward, Ph.D., Jon Lawrie, Ph.D., Walter King, Ph.D., and Donald Neil Halbert, Ph.D., upon which its relies to support its Motion for Partial Summary Judgment in accord with the terms of the Protective Order entered in this case.

Dated:_____

_____
JUDGE OF THE DISTRICT COURT

Bonfire Boogie

00 SEP 18 AM 9:53

BY: [signature] DEPUTY

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC. Defendants.	CASE NO. 99CV2668 H (AJB) **PROTECTIVE ORDER** Date: September 15, 2000 Time: 9:30 a.m. Dept.: Courtroom A Trial Date: Not Yet Set

WHEREAS, in the course of this litigation disclosure may be sought of information which a party or third party regards as being of a confidential, trade secret, proprietary, technical, commercial, or financial nature (hereinafter collectively referred to as "Confidential Information"); and

WHEREAS, the parties, GEN-PROBE INCORPORATED ("GEN-PROBE") and VYSIS, INC. ("VYSIS") desire to establish a mechanism to protect the disclosure of Confidential Information:

IT IS HEREBY ORDERED that the following shall govern the disclosure of Confidential Information in this action:

1. All originals or copies of transcripts of depositions, exhibits, answers to interrogatories and requests for admissions, and all documents, materials, tangible things and

information obtained by inspection of files or facilities or by production of documents (hereinafter collectively referred to as "Information") which sets forth, refers to, or contains any Confidential Information, may be designated by the party producing the Information either as "CONFIDENTIAL - [producing party's name]" or as "CONFIDENTIAL - [producing party's name] - ATTORNEYS ONLY" (*i.e.*, "CONFIDENTIAL – GEN-PROBE - ATTORNEYS ONLY" or "CONFIDENTIAL - VYSIS - ATTORNEYS ONLY").

2. Any Information designated as CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY and all Information derived therefrom (excluding such Information as is derived lawfully from an independent source), shall not be disclosed to anyone except as provided in Paragraphs 3, 4 and 5, below, shall be used only for the purposes of this litigation, and shall not be used for any business, financial or other purpose whatsoever.

3. Information designated as CONFIDENTIAL shall not be given, shown, made available or communicated in any way to any person or entity other than the following:

(a) Lawyers for Gen-Probe:

(i) Cooley Godward LLP

(ii) R. William Bowen, Jr.

(iii) Peter R. Shearer

(iv) Christine A. Critzmacher

(b) Lawyers for Vysis:

(i) Finnegan, Henderson, Farabow, Garrett & Dunner LLP

(ii) Wright & L'Estrange

(iii) Norval B. Galloway

(c) Partners, members, associates, or employees of any of the foregoing lawyers assisting in this litigation;

(d) The Court and Court personnel and stenographic reporters at depositions taken in this action;

(e) The following individuals:

(i) Officers, directors and up to three designated employees of GEN-PROBE; **PROVIDED, HOWEVER**, that GEN-PROBE must designate such employees and give notice to VYSIS of such designation not later than 10 days prior to the disclosure of any **CONFIDENTIAL** Information to such person;

(ii) Officers, directors and up to three designated employees of VYSIS; **PROVIDED, HOWEVER**, that VYSIS must designate such employees and give notice to GEN-PROBE of such designation not later than 10 days prior to the disclosure of any **CONFIDENTIAL** Information to such person:

(f) Independent experts or consultants whose substantive advice is or will be used by a party hereto in connection with preparation for trial or trial of this action, as well as any employees, associates or independent contractors retained by those experts to assist in their work on this matter. Counsel desiring to disclose **CONFIDENTIAL** or **CONFIDENTIAL - ATTORNEYS ONLY** Information to such experts or consultants shall first obtain a signed undertaking, in the form of Exhibit A attached hereto, from each such expert or consultant. Such Information will not be disclosed to any such expert or consultant for a period of ten (10) days after service by facsimile, Federal Express or other next day mail of the signed undertaking upon opposing counsel. Proposing counsel shall also provide opposing counsel with information regarding the identities of the proposed experts or consultants, including their names, address and job titles, the name and addressees of their employers and a current curriculum vitae including a list of all persons or entities for whom such persons consulted or from whom they received income directly or indirectly during the prior four (4) years:

(g) Any person that originally authored or received the document, or gained knowledge of the Information it contains in the regular and ordinary course of business; and

(h) Independent contractors retained to assist with non-substantive aspects of the preparation for trial or trial of this litigation (e.g., copying services, graphics services, jury consultants, etc.).

4. Information designated as **CONFIDENTIAL - ATTORNEYS ONLY** shall not be given, shown, made available or communicated in any way to any person or entity other than those persons described in paragraphs 3(a), 3(b), 3(c), 3(d), 3(f), 3(g), and 3(h) above.

5. Third party discovery in this proceeding may involve disclosure of Confidential Information, which if designated in conformity with the provisions of this Order, shall be subject to the provisions herein and provide the non-party with all of the rights and obligations set forth herein. In order to expedite third party discovery, a copy of this Order and a letter generally informing the third party of its right to invoke the protections set out herein shall be served with all such discovery.

6. In the event that a producing party inadvertently fails to designate Information **CONFIDENTIAL** or **CONFIDENTIAL ATTORNEYS ONLY** or incorrectly so designates Information, that party may make a late designation or change the designation by so notifying in writing all parties to whom the Information has been disclosed. The receiving parties shall take reasonable steps to ensure that the Information is thereafter treated in accordance with the designation. Late designation shall not be deemed a waiver of the confidential status of the late designated Confidential Information. No person or party shall incur any liability hereunder with respect to disclosure that occurred prior to the receipt of written notice of belated designation.

7. If an opposing party desires to object to the submission of **CONFIDENTIAL** or **CONFIDENTIAL ATTORNEYS ONLY** Information to individuals identified in paragraph 3(f), it shall notify the proposing party in writing and by facsimile transmission (with original sent by First Class Mail), within the ten (10) day period referred to in paragraph 3(f) of its objection and the

grounds therefore. If no such objection is made in such time and manner, the proposing party may disclose CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY Information to such person subject to the subsequent provisions in this paragraph. If an objection is properly made and the dispute is not resolved on an informal basis between the proposing and objecting party, the proposing party shall, within twenty (20) days after such written objection, submit the matter on motion to the Court for ruling. In the event of such written objection, the proposing party shall withhold disclosure of CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY Information to the objected individuals pending the ruling of the Court or written agreement between the parties to the dispute.

8. The attorneys of record shall maintain a file of all written agreements signed by persons to whom they have given materials designated as CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY. Said file shall be made available upon request for inspection and copying by any attorney of record.

9. Counsel shall not disclose Information designated as CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY to a witness testifying at a deposition except in strict conformity with the provisions of this Order. No such disclosure shall be made to any witness unless that witness is entitled by this Order to receive that Information or the party that produced that Information assents to the disclosure of such Information in writing or on the record of the deposition. If, during the course of any deposition, (a) an attorney of record for any party desires to make inquiry into Information subject to the designation CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY, or (b) an attorney of record for a party asserts that an answer to a specific inquiry is subject to the foregoing designations, the attorney shall make such inquiry only in the presence of those persons authorized access to such Information. Such testimony shall be sealed, and the parties hereto shall treat it subject to the provision for disclosure set forth herein. Nothing in this paragraph shall preclude counsel at a deposition of a party witness from disclosing to the party witness confidential information produced by that party.

10. All testimony elicited during depositions, hearings, and other proceedings shall be deemed **CONFIDENTIAL – ATTORNEYS ONLY** until the expiration of thirty (30) days after the mailing or after delivery of a copy of the transcript of the testimony by the court reporter to counsel who requested a copy of the transcript. This paragraph will not otherwise affect the deposition, hearing or other proceeding which is being recorded while it is in session. Within the thirty-day period following such mailing of the transcript, any party may, by written notice served on all parties, designate all or any portion of the testimony to be **CONFIDENTIAL** or **CONFIDENTIAL - ATTORNEYS ONLY**. The right to make such designation shall be waived unless made before the end of the thirty-day period. Upon being informed that certain portions of a transcript are designated as **CONFIDENTIAL** or **CONFIDENTIAL - ATTORNEYS ONLY**, each party must cause each copy in their custody, possession or control to be so marked immediately.

11. Any court reporter who transcribes testimony in this action at a deposition shall agree, before transcribing any such testimony, that all **CONFIDENTIAL** and **CONFIDENTIAL - ATTORNEYS ONLY TESTIMONY** is and shall remain confidential and shall not be disclosed except as provided under this Order and that copies of any transcript, reporter's notes or any other transcription records of any such testimony shall be retained in absolute confidentiality and safekeeping by such shorthand reporter or shall be delivered to an attorney of record or filed with the Court.

12. Interrogatory answers and answers to requests for admissions designated as **CONFIDENTIAL** or **CONFIDENTIAL - ATTORNEYS ONLY** shall be delivered to the attorney of record propounding the interrogatories or requests without being filed with the Court unless required in any further proceedings herein. When documents so designated and/or other matters of the same or similar nature are the subject of inquiry at depositions, the portion of the transcript which sets forth or contains Information about such, together with such documents, shall be sealed and shall not be filed with the Court unless required in any further proceedings herein.

13. No Information that was designated previously as **CONFIDENTIAL** or **CONFIDENTIAL - ATTORNEYS ONLY** will be filed with the Court unless it is filed under seal. To

comply with this requirement, CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY Information must be filed in sealed containers labeled with: (1) the title to this action; (2) the general nature of the contents; (3) the words CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY; and (4) a statement substantially in the following form:

> CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER. This sealed container filed in this case. *Gen-Probe Incorporated v. Vysis, Inc.*, United States District Court, Southern District of California Case No. 99cv2668H (AJB), contains confidential materials, which may be used only in connection with the prosecution or defense of this lawsuit. Pursuant to Protective Order, the container shall not be opened nor the contents thereof revealed except to the Court. After any such opening or revelation, the container shall be resealed with the contents inside.

Nothing shall be filed under seal, and the court shall not be required to take any action, without separate prior order by the judge before whom the hearing or proceeding will take place, after application by the affected party with appropriate notice to opposing counsel.

14. Should an attorney of record for any party desire to use Information designated as CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY, or any summary thereof or excerpt therefrom, during the trial of or at any hearing in this action, counsel shall, prior to such use, bring the confidentiality thereof to the attention of the Court and/or the party which designated the Information. Counsel for the producing party may request that any portion of the transcript or exhibit containing such Information be filed under seal with the Court, and be accorded protection as provided by the terms of this Order. All persons present at the time of such use shall be directed to treat such Information as Confidential Information, and counsel for the parties shall exercise all reasonable care not to disclose such materials needlessly in the public record of this proceeding nor to persons not entitled under this Order to receive such Information.

15. The designation by counsel for the disclosing party of any Information as constituting Confidential Information is intended solely to facilitate the preparation and trial of this case, and such designation shall not be construed in any way as an admission or agreement by any

party that the designated disclosure constitutes or contains any Confidential Information in contemplation of law.

16. Within sixty (60) days of the final disposition of this action, whether by judgment (including exhaustion of all appeals), settlement or otherwise each attorney of record shall promptly deliver to the party or witness from whom obtained either (1) all items which have been marked CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY and all copies made thereof or (2) an affidavit sworn under penalty of perjury declaring that all such items and all copies thereof have been destroyed. However, the law firm of each attorney of record may retain one record copy of any items filed with the Court upon notice to the other attorneys of record of such retention and subject to the terms of this Order.

17. If a party desires to object to the designation of CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY as applied to specific Information, it shall serve its objections in writing and by facsimile transmission (with original sent by First Class Mail). If the objections are not resolved on an informal basis between the designating party and the objecting party, the objecting party may, within twenty (20) days after service of such written objection, submit to the Court for ruling a noticed motion to be relieved entirely or in part from the provisions of this Order.

18. In the event anyone shall inadvertently disclose Information another party or third party has designated CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY, the party making the inadvertent disclosure shall, upon learning of the disclosure:

(a) Promptly notify the person to whom the disclosure was made that the disclosure contains Confidential Information;

(b) Promptly make all reasonable and necessary efforts to obtain the return of and preclude dissemination or use of the Confidential Information by the person to whom disclosure was inadvertently made; and

(c) Immediately notify the producing party of the identity of the person to whom the disclosure was made, the circumstances surrounding the disclosure, and the steps that

have been taken and will be taken to ensure against further dissemination or use of the Confidential Information.

19. In the event anyone shall violate, or threaten to violate, any terms of this Order, the parties hereto agree that the aggrieved party may immediately apply to obtain injunctive relief against any such person, and in the event the aggrieved party shall do so, the respondent person, subject to the provisions of this Order shall not employ as a defense thereto or claim that the aggrieved party possesses an adequate remedy at law.

IT IS SO ORDERED.

Dated: _____

_____
JUDGE OF THE DISTRICT COURT

EXHIBIT A

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC., Defendant.	No. 99cv2668 H (AJB) UNDERTAKING

I, _____, declare and say that:

1. I _____ live at _____ _____ _____ _____ _____ _____.

2. I am employed as _____ by _____ _____ _____ _____.

3. I have read the Protective Order entered *Gen-Probe Incorporated v. Vysis, Inc.*, Case No. 99cv2668 H (AJB), and a copy of the Protective Order has been given to me.

4. I agree to be bound by the terms of the Protective Order, and agree that any Information designated as CONFIDENTIAL or CONFIDENTIAL - ATTORNEYS ONLY within the meaning of the Protective Order, will be used by me only to assist counsel in connection with the above-referenced litigation.

5. I agree that I will not disclose or discuss Information designated as **CONFIDENTIAL** with anyone other than the persons described in Paragraph 3 of the Protective Order.

6. I agree that I will not disclose or discuss Information designated as **CONFIDENTIAL - ATTORNEYS ONLY** with anyone other than the persons described in paragraph 4 of the Protective Order.

7. I understand that any disclosure or use of Information designated as **CONFIDENTIAL** and **CONFIDENTIAL – ATTORNEYS ONLY** in any manner contrary to the provisions of the Protective Order will subject me to sanctions for contempt of the Court's Order.

8. I agree to be subject *in personam* to the jurisdiction of the United States District Court for the Southern District of California in connection with any proceeding relating to the enforcement of the Protective Order.

I declare under penalty of perjury that the foregoing is true and correct and that this declaration was executed this _____ day of _____, 2000, at _____.

_____

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UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

CIVIL ACTION NO. 99CV2668 H (AJB)

GEN-PROBE, INCORPORATED

Plaintiff

v.

VYSIS, INC.

Defendant

- - - - - - - - -

Deposition of Anthony J. Janiuk

Wednesday, May 16, 2001

1:33 p.m.

Hale and Dorr, LLP

60 State Street

Boston, Massachusetts

- - - - - - - - -

Reporter: Deborah Roth, RPR

EXH 13 PAGE 5

Q. The next entry on this page is a reference to an Amoco method.

Based on your experience as an attorney with Amoco or Gene-Trak, are you able to draw any inferences about what method of amplification is referred to there?

MR. LIPSEY: Same objection.

A. I have not seen this. I was not party to this -- I was not at this partnership meeting. I do not know what was discussed.

Q. And to the best of your recollection -- you have not seen this document -- you can't recall ever having heard these terms while you worked at Amoco or Gene-Trak?

A. I have not heard anything spoken of as "the Amoco method" or "the Gene-Trak method."

Q. And you're not able to form any belief about what method of amplification might have been described by those terms or referred to by those terms?

A. No.

Q. To the extent you had interactions with Dr. Richards at Amoco and Gene-Trak, did he seem to have a basic understanding of patents?

14:11:58 A. Dr. Richards was not a patent attorney. He
14:12:06 often did not use words and phrases that we in --
14:12:17 that patent attorneys used, correctly.
14:12:22 He had -- was an intelligent man
14:12:32 technically, very good person, and he could deal
14:12:39 with intellectual property issues reasonably well.
14:12:46 He usually would seek counsel on most
14:12:50 things that involved patent law issues.
14:12:58 Q. I think you recalled a general impression
14:13:01 that Dr. Richards sometimes did not use words or
14:13:03 phrases correctly in a technical sense as a patent
14:13:10 lawyer might. Can you recall any particular
14:13:10 instances where he had that problem?
14:13:21 A. No. That has to do with my experience
14:13:24 working with him.
14:13:28 Q. But in terms of a particular instance, you
14:13:32 can't give me an example?
14:13:33 A. No.
14:13:39 Q. And I think you told me that it was
14:13:42 Dr. Richards' custom when dealing with important
14:13:47 matters to seek advice from patent counsel?
14:13:50 MR. LIPSEY: I object to the form. Lack
14:13:50 of foundation.
14:13:53 A. I think that he generally did, yes.

no.

Q. I would like you to look at Exhibit 143, please.

MR. BOWEN: What I will ask to be marked Exhibit 143.

(Exhibit No. 143 was marked.)

Q. Exhibit 143 is a letter dated November 14, 1989 to Dr. Richards. Your name is typed at the bottom. It appears that someone may have signed the letter for you.

Did somebody else sign the letter for you?

A. I don't have any present recollection of this letter, but it's on my letterhead, and it could very well have been sent out to Dr. Richards at Gene-Trak Systems.

MR. LIPSEY: That wasn't quite the question he asked you.

A. What is it?

Q. Do you think somebody else signed the letter for you?

A. I think that's my secretary's signature signing my name, and I think that would have been at my instruction, yes, sir.

Q. At one point in time did you have a secretary whose initials were "VAY"?

A. I had I think a secretary named Vickie.

Q. That's only 12 years ago. Come on.

A. I don't know what her last name was. Vickie -- I think I had a secretary Vickie.

Q. As you sit here, do you think it's likely that Exhibit 143 was prepared at your request and sent to Dr. Richards?

MR. LIPSEY: I object to the form.

A. I think that this letter was probably sent at my instruction and did what it purports to have done.

Q. Do you recall why you sent Dr. Richards a copy of the '920 application in November of 1989?

A. Are you questioning the date or why I sent it to Dr. Richards?

Q. Why.

A. Why I sent it to Dr. Richards?

I would have sent to it to Dr. Richards, because I think this would have been one of the assets that Amoco would have been contributing to Gene-Trak Systems as part of the joint venture.

Q. Can you recall any conversations with

0000 0000 0000 0000

Gen-Probe versus Vysis. Witness David Ward, 89 Quail Run Madison, Connecticut 06443.

THE VIDEOGRAPHER: We are now on record. This is the deposition of Dr. David Ward taken on behalf of the plaintiff in the case of Gen-Probe, Inc. plaintiff versus Vysis Inc. Case number C A 99 CV 2 66 8. Filed in the United States District Court, Southern District of California. Today's date is May 18, 2001. The time on videotape record is 9: 39 a.m. This deposition is held at 11 57 Chapel Street, New Haven Connecticut my name is Kevin Aspinwall. Would everyone please introduce yourselves for the record.

MR. BOWEN: William Bowen for plaintiff Gen-Probe Inc.

MR. LIPSEY: Defendant defendant if I RRS.

Witness sworn

BY MR. BOWEN:.

Q. Would you please state your name?

A. David Ward.

Q. Dr. Ward, this deposition is being taken in connection with a patent case that

activities that he was involved in but I didn't, I can recall whether that was his title.

Q. Did you have an impression during the period of time that you were associated with Gene-Trac that Dr. Richards was knowledgeable with respect to the technology used by Gene-Trac?

A. Yes.

Q. He seemed knowledgeable to you about nucleic acid hybridization technologies?

A. Yes.

Q. Have you ever heard the term one of ordinary skill in the art?

A. Yes.

Q. And do you have -- you have been an expert in a fair number of patent cases is that true?

A. Some.

Q. And in the course of those cases have you had the term one of ordinary skill in the art?

A. Yes.

Q. Based on your impression of Dr.

Richards while you were associate with with Gene-Trac, did you consider him to be one of ordinary skill in the art in the area of nucleic acid hybridization.

MR. LIPSEY: I object to the form calls for an expert opinion.

A. Can you rephrase the question.

Q. I am not sure I can. I am asking whether or not based on your impression and knowledge of Dr. Richards whether you considered him to be one in the ordinary skill in the art of nuclear hybridization.

MR. LIPSEY: Same objection.

A. The answer is he had knowledcge in the area.

Q. I would like you to look at what has been previously marked as Exhibit 45. I am turning these pages only for you because the notebook didn't survive the trip from California too well. Sorry.

And this is a document Exhibit 45 that is entitled partnership committee meeting August 27, 1987. Would you take a moment and look at that please. And I would like you to look at so you can tell me

IN THE UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

- - - - - - - - - - - - - - -X

GEN-PROBE INCORPORATED,

Plaintiff,

VS.

VYSIS, INC.,

Defendant.

- - - - - -- - - - - - - - X

NO.99cv2668 H (AJB)

CONFIDENTIAL

Videotaped Deposition of
JONATHON MICHAEL LAWRIE, Ph.D.
Durham, North Carolina
Thursday, February 15, 2001

Reported by:
Sydney C. Silva, Registered Professional Reporter
File No:

COPY

EXH 16 PAGE 16

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meeting of Scientific Advisory Board in the fall of 1986? 11:45:52 11:45:56
A. I don't remember. 11:45:57
(Deposition Exhibits Nos. 49 and 50 marked for identification.) 11:46:16 11:46:16
Q. I'm going to hand you two sets of notes. The first set we'll mark as Exhibit 49 and the second set we'll mark as Exhibit 50. And I would like you to look at them, first so you can tell me whether or not you recognize any of the handwriting on these two exhibits. 11:46:16 11:46:17 11:46:22 11:46:29 11:46:33 11:46:36
A. Yes, I do. 11:46:39
Q. Do you recognize the handwriting on both? 11:46:40
A. Yes. 11:46:43
Q. Exhibit 49 has got the larger, clearer printing and a schematic on the first page. Do you know whose handwriting that was? 11:46:45 11:46:50 11:46:54
A. Yes. 11:46:55
Q. Whose? 11:46:56
A. That's mine. 11:46:56
Q. Exhibit 50, do you know whose handwriting that is? 11:46:58 11:47:00
A. Yes. 11:47:01
Q. Whose is that? 11:47:01

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A. It's mine. 11:47:02
Q. Both of these are in your handwriting? 11:47:03
A. Yes. 11:47:08
Q. And to the best of your recollection, were these Exhibits 49 and 50 prepared in the course of a Scientific Advisory Board meeting? 11:47:09 11:47:12 11:47:16
A. My best of my recollection or looking at the documents? 11:47:19 11:47:25
Q. The best of your recollection. 11:47:26
A. I don't know what these were made for. 11:47:27
Q. Okay. Looking at Exhibit 50, do you think that was prepared in the course of a Scientific Advisory Board meeting? 11:47:29 11:47:31 11:47:34
A. Yes, it says "SAB." 11:47:36
Q. And do you -- the heading at the top of Exhibit 50, "SAB" indicates it was prepared by you as notes of a Scientific Advisory Board meeting at Gene-Trak? 11:47:39 11:47:43 11:47:45 11:47:48
MR. BANKS: Could you read that back, please. 11:47:49 11:47:51
Q. I'll try it again, it'll be easier. 11:47:51
Looking at Exhibit 50, it is headed at the top of Page 1, "SAB." Do you see that? 11:47:54 11:47:58
A. Yes is. 11:48:01

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Q. Does that indicate to you that Exhibit 50 was prepared by you in the course of a Gene-Trak Scientific Advisory Board meeting? 11:48:01 11:48:04 11:48:08
A. During the meeting? 11:48:09
Q. Yes. 11:48:10
A. I don't know. 11:48:11
Q. Prepared in connection with the meeting? 11:48:12
A. Yes. 11:48:13
Q. Could have been prepared before or during or after a meeting? 11:48:14 11:48:17
A. Yes. 11:48:18
Q. Do you recall which one? 11:48:19
A. Hum. I don't know. 11:48:24
Q. Do you have any idea when you prepared Exhibit 49? 11:48:29 11:48:33
A. When? I don't know. 11:48:42
Q. Can you recall an event that you prepared Exhibit 49 in connection with? 11:48:47 11:48:52
A. No. 11:48:53
Q. You can't do anything to place Exhibit 49 in context as you sit here today? 11:48:53 11:48:56
A. It's neat, so it was prepared before a presentation; but I have no idea what presentation. 11:48:59 11:49:03
Q. Whatever presentation you made that included Exhibit 49, you believe Exhibit 49 was prepared ahead of time prior to the presentation? 11:49:08 11:49:11 11:49:15
A. Yes. 11:49:18
Q. Can you recall getting the input of anyone in connection with the preparation of Exhibit 49? 11:49:19 11:49:20 11:49:24
A. No. 11:49:26
Q. Exhibit 50, would you say that's less neat than Exhibit 49? 11:49:27 11:49:29
A. Yes. 11:49:30
Q. Would that indicate to you that it might be -- let me start over. 11:49:31 11:49:35
Would that indicate to you that it is more likely notes taken contemporaneously during a meeting at the same time the meeting was going on? 11:49:37 11:49:40 11:49:45
A. I don't know. 11:49:52
Q. Do you have any independent recollection of Exhibit 49; can you recall having seen it before? 11:49:53 11:49:55 11:49:58
A. No. 11:50:00
Q. Do you recall any meeting of the Scientific Advisory Board of Gene-Trak at which there was a discussion of combining target capture with target amplification? 11:50:05 11:50:06 11:50:10 11:50:14

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PCR method? 12:13:08
A. I don't know. I don't know. 12:13:15
Q. You can't recall whether you were ever, 12:13:16
whether you were ever concerned about that? 12:13:20
A. Correct. 12:13:22
Q. Can you recall whether anyone else -- 12:13:23
that you understood that anyone else was concerned 12:13:24
about whether the use of specific capture probes 12:13:26
made any work that Gene-Trak was doing too close to 12:13:31
Cetus's PCR method? 12:13:34
MR. BANKS: Just caution you not to 12:13:36
reveal any privileged information in answering 12:13:38
that. 12:13:42
A. Yeah. Capture probes are not the same as 12:13:42
Cetus; so I don't think, my definition of capture 12:13:45
probes is not Cetus. Even today I would say it is 12:13:48
different. 12:13:54
Q. Can you ever recall discussions at 12:13:58
Gene-Trak about trying to achieve target 12:14:01
amplification that was equivalent to PCR by 12:14:05
combining a specific capture within a nonspecific 12:14:09
amplification step? 12:14:14
A. Equivalent to Cetus? No. 12:14:20
Q. Better than Cetus? 12:14:22

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A. Better? Yeah, it's difficult. 12:14:29
Q. While you were at Gene-Trak, did 12:14:36
Gene-Trak do work that combined specific target 12:14:38
capture with amplification methods that would be 12:14:41
nonspecific in and of themselves? 12:14:45
A. So you, by "develop," you mean? 12:14:51
Q. Was there work going on -- 12:14:55
A. I don't know. 12:14:57
Q. -- in the laboratory? 12:14:57
Looking at Page 5 of Exhibit 49, which 12:15:04
you will probably be happy to know is the last page 12:15:11
of Exhibit 49, Page 5 lays out apparently to me 12:15:14
three alternative methods of signal amplification. 12:15:22
Is that a fair statement? 12:15:24
A. Three? Three bullet points, yes. 12:15:27
Q. These are three method of signal 12:15:31
amplification? 12:15:34
A. Let me look. Yes. 12:15:35
Q. We looked, I think, at five pages in 12:16:05
Exhibit 49. The fifth page has got three methods 12:16:09
of amplification; the others generally I think 12:16:13
describe one. Is that fair? 12:16:15
A. Yes. 12:16:17
Q. Can you relate any of those five methods 12:16:17

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diagramed out in Exhibit 49, any of those five 12:16:20
pages, to any of the amplification methods set 12:16:24
forth on the third page of the Exhibit 48, which is 12:16:29
the Scientific Advisory Board packet from 12:16:37
November 4, 1986? 12:16:40
A. Orgel. I, I could speculate that the Q 12:16:55
beta here is similar to what is set here. This 12:17:01
says "signal amplification" on top and "Q beta." 12:17:05
This says Q beta replicase and signal 12:17:10
amplification. 12:17:12
Q. So you think the Q beta signal 12:17:12
amplification on Page 5 of the package of diagrams 12:17:15
is probably two Orgel? 12:17:21
A. This? That I can't say. I don't -- I 12:17:23
can't remember what Orgel is. 12:17:24
Q. Can you relate any of the methods shown 12:17:27
on the Scientific Advisory Board packet to any of 12:17:30
the methods shown in Exhibit 49, the package of 12:17:33
diagrams? 12:17:40
A. There's lots of good stuff here. I'd 12:17:52
have to speculate. Beyond Orgel, which I assume is 12:18:03
the same as Kramer, I would be speculating to say 12:18:07
that this is part of that. 12:18:10
MR. BOWEN: We could go another five 12:18:21

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minutes or break for lunch, what's your 12:18:23
preference? 12:18:26
MR. BANKS: I'm ready to break whenever 12:18:28
you want to, but it's your call. 12:18:29
MR. BOWEN: Are you ready? 12:18:34
THE WITNESS: Doesn't matter to me. 12:18:35
MR. BANKS: Do you want to break for 12:18:35
lunch? 12:18:36
THE WITNESS: We can go another five 12:18:37
minutes, if you want to complete your chain of 12:18:39
thought. 12:18:43
BY MR. BOWEN: 12:18:43
Q. Then I would like for you to pick up the 12:18:44
patent that we marked at the start as Exhibit 37. 12:18:46
A. Okay. 12:18:49
Q. We previously looked at I think Example 6 12:18:50
of the patent, which is in Column 31, starts in 12:18:53
Column 31. I would like to turn back to earlier in 12:18:56
the patent, Column 24, the prior page of the 12:19:01
patent, and start with Example 1. 12:19:06
A. All right. 12:19:19
Q. You know, that's going to take too much 12:19:25
time. 12:19:29
Can you turn to Example 7, which is in 12:19:39

A. Yes, in the first sentence. 16:19:36

Q. And the amplification method described in Example 4 is in vitro amplification of captured DNA using an RNA polymerase, is that right? 16:19:45 16:19:51 16:19:56

A. Yes. 16:20:07

Q. And is it your understanding that the use of the RNA polymerase would result in nonspecific transcription of the target DNA? 16:20:10 16:20:14 16:20:23

A. Yes. 16:20:25

Q. So Example 4 describes a nonspecific method of amplification? 16:20:25 16:20:29

A. Yes. 16:20:33

Q. And the method of amplification described in Example 4 is a method of linear amplification, is that correct? 16:20:34 16:20:37 16:20:43

A. Yes. 16:20:47

Q. Looking at Example 5, Example 5 also refers to nonspecific amplification, is that correct? 16:20:56 16:21:10 16:21:13

A. The first sentence says, "Nonspecific replication of target DNA and transcription of that DNA are used to amplify captured target DNA." So it does address amplification. 16:21:13 16:21:17 16:21:23 16:21:36

Q. And the amplification method disclosed in 16:21:38

Example 5 is a linear method? 16:21:41

A. Let's see. 16:21:44

Yes, it is linear. 16:22:29

Q. So Example 5 discloses a linear nonspecific method of amplification? 16:22:31 16:22:34

A. Yes. 16:22:37

Q. So recapping the examples, Examples 1 through 3 disclose capture methods without amplification? 16:22:38 16:22:43 16:22:46

A. Yes. 16:22:48

Q. And Example 4 discloses linear nonspecific amplification? 16:22:49 16:22:53

A. Yes. 16:22:54

Q. Example 5 discloses linear nonspecific amplification? 16:22:55 16:22:59

A. Yes. 16:23:00

Q. Example 6 seeks to describe nonspecific exponential amplification? 16:23:02 16:23:10

A. Let's see. Yes. 16:23:13

Q. And Example 7 describes -- seeks to describe nonspecific exponential amplification? 16:23:18 16:23:22

A. Yes. 16:23:28

Q. Looking back at Column 30, specifically at Lines 30 through 40, which I think is two 16:23:44 16:23:48

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,)

Plaintiff,)

vs.)No. 99cv2668 H (AJB)

VYSIS, INC.,)

Defendant.)

The confidential deposition of WALTER KING, Ph.D., called as a witness for examination, taken pursuant to the Federal Rules of Civil Procedure of the United States District Courts pertaining to the taking of depositions, taken before ANDREA L. CARTER, a Notary Public within and for the County of Cook, State of Illinois, and a Certified Shorthand Reporter of said state, CSR No. 84-3722, at Suite 205, 2111 Butterfield Road, Downers Grove, Illinois, on the 18th day of April, A.D. 2001, at 9:01 a.m.

you, Drs. Halbert, Lawrie and Collins?

A. How many subject matters?

Q. Yes. When we get done with this inquiry, I want you to be able to tell the ladies and gentlemen of the jury absolutely everything you can remember being discussed during the course of that meeting. But what I wanted to try to do to ease it for you hopefully, if that's the case, is start with the high level subject matters.

From a high level perspective, what were the discussion topics addressed during this meeting?

A. I think that at the highest level we were looking for amplification methods that did not involve PCR amplification.

Q. Why? Why were you looking for amplification methods to begin with?

A. Well, at the time that we formed this joint venture, Gene-Trak, Vysis did not have an amplification method, a licensed amplification method. So we felt that it was important that we either seek one out or invent one or have, you know, the ability to demonstrate that we have an amplification method that was different than PCR.

amplification could have ranged from signal amplification to probe amplification as well; is that correct?

MR. BANKS: Objection as to time.

BY THE WITNESS:

A. I am not aware that anybody was working on probe amplification.

BY MR. SWINTON:

Q. Okay. So the purpose -- the general purpose of the discussion as I understand it that took place at Gene-Trak among the four doctors was to identify -- in general identify an amplification technique that would amplify low concentrations of target nucleic acids in a sample, correct?

A. Yes.

Q. And as I understand your testimony, you wanted to find a technique that was different from PCR, correct?

A. Yes.

Q. Why? Why did you want to find something that was different than PCR?

A. Well, I wasn't involved in the business development part. I think that I was asked to put

correct?

A. I am not sure. I am not sure that that's true.

Q. Did you undertake any investigation in order to verify your belief that you were the sole -- one of the sole inventors of nonspecific amplification techniques?

MR. BANKS: Object to form.

BY THE WITNESS:

A. No.

BY MR. SWINTON:

Q. So you don't know one way or the other?

A. No.

Q. Okay. At the time that the four of you participated in the filing of the original application that led to the issuance of -- that disclosed amplification techniques that led to the issuance of the '338 patent, did you intend to claim the combination of target capture with PCR?

A. I don't have any recollection of that being tied together with PCR.

Q. In fact, wouldn't -- based upon what I have heard this morning, in fact wouldn't that have been inconsistent with the -- the state of mind

Q. Do you believe now that you invented the combination of target capture and PCR?

A. Well, the -- these drawings don't reflect that we combined it with PCR. So I guess I am kind of confused. I -- we are talking about the context of reversible target capture and the methods of detection as stated here. So I am not sure that we even talked about linking this with PCR.

Q. Fair enough. And I don't -- let me just close with it.

Is it fair to summarize that you don't believe that now or at any time in the past that you ever concluded that you invented the combination of target capture with PCR?

A. I would have to do a literature search and see whether there was any prior art. I don't really even know to this date.

Q. Independent of prior art -- I am just asking your state of mind what you thought.

Did you believe that you had come up with the idea of combining target capture with PCR at any time in the work that was associated with the '338 patent?

A. Not specifically with PCR, no.

Q. Did any of the other three identified inventors: Drs. Lawrie, Halbert or Collins ever indicate to you that -- at any point in time, that they ever believed that one of them had come up with the idea of combining target capture with PCR?

A. No, I don't recall.

Q. Would you take a look at Exhibit 41.

Is this a copy of a portion of a lab notebook that you maintained while you were at Amoco?

A. Yes.

Q. And the -- I assume that these are selected pages out of the lab notebook, not the entirety of the book. At least that's what it appears to me.

A. Yes.

Q. And the -- this laboratory notebook encompasses the period of time November 16, 1985 to October 24, 1986?

A. November 16th of '85 to October of '86, yes.

Q. Would this notebook have followed you or would you have taken this on the Gene-Trak or would

Q. Well, you agree you are not changing any of your prior testimony. You didn't talk about target capture and specific amplification in your meeting in 1986, correct? That's still your testimony?

A. Yes.

Q. And as I recall, you didn't have any further activity with respect to this patent application before you signed the oath in 1997, correct?

A. I didn't have any what?

Q. Did you didn't have any further involvement with respect to any of the work that related to this patent application until you signed the oath in December of 1997, correct?

A. Yes.

Q. All right. And so you didn't talk about -- you did not talk about the combination of target capture and PCR in 1986. It doesn't come up, you didn't have any other discussions about that combination before you signed the oath in December 1997, and the only specific amplification technique you are aware of in December 1997 was PCR, correct?

A. Specific amplification?

Q. Yes.

A. Yes.

Q. So your testimony now is in December 1997 you believed your invention encompassed as to specific amplification, the combination of target capture and PCR. Is that your testimony now?

A. It encompasses that, yes.

Q. Why isn't there any disclosure in the specification of the 338 patent that addresses PCR?

MR. BANKS: Objection, asked and answered.

MR. SWINTON: Well, I have got different questions and different answers before.

MR. BANKS: You just asked it two minutes ago.

BY MR. SWINTON:

Q. Why isn't there any disclosure in the specification of the '338 patent of PCR?

A. Well, you were asking me about line 2 to see whether it includes specific and nonspecific amplification very early on in this, and I said that my reading of it was that did it include specific amplification.

So why we didn't give an example of PCR? I don't know. We were trying -- you said from a

very high level meeting, the very high level meeting I stated that we were trying to find ways around just PCR the way it was being practiced. So PCR was already on our mind. As to why we didn't think of an example? We were trying to think of these more novel examples.

Q. Didn't there come a time as you sat in your office in December of 1997 you are reviewing the application and you read all of the examples you have that deal with nonspecific amplification, and you thought, gee, since I am going to claim the combination of target capture and PCR, why don't we include something, just something, even a passing reference to PCR in the specification. Didn't that thought ever come to mind before you signed the oath claiming that this was your application?

A. I guess not. I mean, I don't recall making -- having that thought or telling anybody.

MR. SWINTON: No further questions.

MR. BANKS: I have nothing more.

THE VIDEOGRAPHER: Going off the video record at 3:12 p.m. at the end of tape 3.

FURTHER DEPONENT SAITH NOT.

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,)

Plaintiff,)

vs.)No. 99cv2668 H (AJB)

VYSIS, INC.,)

Defendant.)

The confidential deposition of DONALD NEIL HALBERT, Ph.D., called as a witness for examination, taken pursuant to the Federal Rules of Civil Procedure of the United States District Courts pertaining to the taking of depositions, taken before ANDREA L. CARTER, a Notary Public within and for the County of Cook, State of Illinois, and a Certified Shorthand Reporter of said state, CSR No. 84-3722, at 100 Abbott Park Road, Abbott, Illinois, on the 19th day of April, A.D. 2001, at 10:17 a.m.

Q. At least as to the four -- the Examples 4 through 7, is there any information or reference with respect to those examples that you would characterize to suggest specific amplification?

A. To suggest specific amplification?

Q. Yes.

A. Not to my knowledge.

Q. Of any of the examples, not just limited to Examples 4 through 7, but for any of the examples 1 through 7, is there any -- any information associated with those four examples in the '338 patent that you recognize to be the result of any experimental work that you conducted while at either Gene-Trak or Amoco?

A. That I recognize as being the result of my own experimental work?

Q. Yes, sir.

A. I don't have clear enough recollection of that.

Q. And my question was that limited, but let me expand it a little bit.

Do you recognize anything about Examples 1 through 7 that you recognize to be the result of experimental work that you supervised while you

EXHIBIT C

Exhibit C Filed Under Seal

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99CV2668 H (AJB)

PLAINTIFF GEN-PROBE INCORPORATED'S REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept: Courtroom 1

[FILED UNDER SEAL]

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While characterizing Gen-Probe's motion as "frivolous," (Vysis Opp. Memo at 2:1), Vysis does not seriously dispute the facts relevant to the Court's determination of Gen-Probe's motion.[1] Significantly, Vysis admits that Gen-Probe does not literally infringe the claims of the '338 patent if the claims cover only non-specific amplification. (Undisputed Fact No. 28.)

Vysis makes two primary arguments to support its assertion that the '338 patent covers specific amplification. First, Vysis contends that a single parenthetical statement in Example 5 of the specification discloses specific amplification. However, each inventor has *admitted* that Example 5 discloses only *non-specific* amplification. Further, the patent expressly states that in the method of Example 5 (and associated Figure 5) the target nucleic acids are replicated "non-specifically."

Second, Vysis contends that the prosecution history demonstrates that the patent encompasses specific amplification methods such as PCR. However, the self-serving arguments first made by Vysis' patent prosecution counsel *in December 1995*, eight years after the patent application was first filed, cannot expand the description of the invention originally set forth in the patent specification.

I. THE CLAIMS OF THE '338 PATENT MUST BE CONSTRUED BASED ON THE "WRITTEN DESCRIPTION" OF THE INVENTION SET FORTH IN THE SPECIFICATION

The specification of every patent must "contain a written description of the invention." 35 U.S.C. § 112; *see also* 3 Chisum on Patents, Adequate Claims § 7.01 *et seq.* The written description requirement protects the public from over-claiming by inventors who have not made an invention that is commensurate with the scope of their claims: "The purpose of this [written description] provision is to ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art *as described in the patent specification.*" *Reiffin v. Microsoft Corp.*, 214 F.3d 1342, 1345 (Fed. Cir. 2000) (emphasis added). Thus, an inventor is entitled to claim only the invention described in the specification.

///

[1] Vysis does not dispute Facts 1, 3, 6, 7, 10-15, 17, 21, 22, or 26-28. Vysis "disputes" Facts 5, 8, 9, 16, 18 only on the ground that Example 5 of the patent discloses specific amplification.

The purpose of claim construction is to interpret the normally terse language found in patent claims. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1580 (Fed. Cir. 1991). Because of the written description requirement, the patent specification is the single best guide to the meaning of a disputed term and is usually dispositive. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). In claim construction, the court gives effect to the written description by determining what a person skilled in the art would have understood to be the invention described in the specification, as of the *earliest* date to which the patent claims priority. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979, 985-986 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996); *accord, Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1472, 1478 (Fed. Cir. 1998). Claims in a patent may not be validly construed to be broader than the supporting disclosures of the specification. *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir.1998).

II. THE SPECIFICATION OF THE '338 PATENT TEACHES ONLY THAT A TARGET CAPTURE STEP WILL IMPROVE *NON-SPECIFIC* AMPLIFICATION

The '338 patent is directed solely to methods of non-specific amplification. The patent specification teaches that a target capture step improves non-specific amplification. The specification describes only the combination of target capture and non-specific amplification. The patent does *not* describe specific amplification methods and does not teach any benefits from the combination of target capture and specific amplification. The specification refers to specially tailored primers only to state that they are not necessary when an initial target capture step is used[2]. The specification is entirely consistent with the inventors' testimony that they were searching for, and invented, *alternatives* to specific amplification (see discussion, *infra*, section III).

In an effort to identify *some* reference to specific amplification in the patent, Vysis can only point to a single parenthetical sentence at the end of Example 5 of the '338 patent[3]. Vysis

---

[2] The invention of the '338 patent cannot encompass methods that the specification states are unnecessary due to the benefits of a target capture step prior to amplification. *Evans Medical Ltd. v. American Cyanamid Co.*, 11 F. Supp. 2d 338, 355-56 (S.D.N.Y. 1998), *aff'd without op.*, 215 F.3d 1347 (Fed. Cir. 1999).

[3] Vysis admits that six of the seven examples in the patent do not disclose specific amplification. (Undisputed Facts Nos. 3, 5-7, 10-13.)

argues that this parenthetical statement discloses use of a specific capture probe as a specific primer, and that thus Example 5 discloses "specific amplification." (Vysis Opp. Memo at 9-10.) However, Vysis' effort to expand the import of this "alternative," parenthetical statement is contradicted by the clear language of the specification and the inventors' testimony about what is disclosed in Example 5.

It is beyond reasonable dispute that Example 5 teaches only the combination of target capture with *non-specific* replication. Example 5 is set forth in three paragraphs of text beginning at col. 31, line 24 of the '338 patent. The first paragraph consists of a single sentence that states, concisely and exactly, what the example teaches:

> In this example, both ***non-specific*** replication of target DNA and transcription of that DNA are used to amplify capture target DNA.

(Exh. 8, at col. 31, ll. 24-54, emphasis added.) The second paragraph of example 5 provides the details of a particular method, and teaches the use of *random* (e.g., non-specific) primers, and non-specific transcription, in the amplification process used in the method. (Exh. 8, at col. 31, ll. 31-33.) As a result of these explicit statements, a person skilled in the art would understand that Example 5 discloses a non-specific method of amplification.

This understanding is reinforced by the fact that Example 5 refers to and incorporates Figure 5 of the drawings included in the patent. (Exhibit 8 at col. 31, l. 28.) The drawings, including Figure 5, are discussed and described in the text of the patent specification:

> In Step 3 of FIGS. 4, 5 and 6, the isolated target is ***non-specifically*** amplified to form a multitude of amplification products.

(*Id.* at col. 15, ll. 56-58, emphasis added.) Thus Vysis' present contention that Example 5 teaches specific amplification is contrary to the multiple descriptions of that example within the specification.

In light of the clear language of the specification, inventors Jon Lawrie and Donald Halbert admitted that Example 5 discloses and teaches only non-specific amplification:

> Q. Looking at Example 5, Example 5 also refers to nonspecific amplification, is that correct?

///

A. The first sentence says, "Nonspecific replication of target DNA and transcription of that DNA are used to amplify captured target DNA." So it does address amplification. . . .

Q. So Example 5 discloses a linear *nonspecific* method of amplification?

A. Yes.

(Lawrie Depo. at 230:17 - 231:16 (Exhibit 9) (emphasis added).)

Q. At least as to the four -- the Examples 4 through 7, ***is there any information or reference with respect to those examples that you would characterize to suggest specific amplification***?

A. To suggest specific amplification?

Q. Yes.

A. Not to my knowledge.

(Halbert Depo. at 94:1-7 (Exhibit 18)(emphasis added).) Dr. Richards reached the same conclusion. (Richards Depo at 139:19 - 140:3 (Exhibit 10).)

Vysis' contention that Example 5 discloses specific amplification is based on the statement, midway through the third (and final) paragraph of Example 5 that: "(Alternatively, the double stranded DNA can be formed by synthesis starting from capture probe a.)" Vysis' retained expert, Dr. David Persing opines that Example 5 discloses specific amplification. However, the mere statement that "the double-standard DNA can be formed by synthesis starting from capture probe a" does not teach that such synthesis constitutes specific amplification nor that the capture probe functions as a specific primer. The term "specific" does not appear in the statement, nor anywhere else in the patent, with respect to primers or amplification. Moreover, inventor Lawrie admitted that use of a capture probe in connection with non-specific amplification does not transform the amplification step into a method of specific amplification such as PCR:

Q. Can you recall whether anyone else -- that you understood that anyone else was concerned about whether the use of specific capture probes made any work that Gene-Trak was doing too close to Cetus's PCR method?

. . . .

///

A. Yeah. ***Capture probes are not the same as Cetus; so I don't think, my definition of capture probes is not Cetus. Even today I would say it is different.***

(Lawrie Depo. at 122: 6-17 (Exhibit 16) (emphasis added).)

The "alternative," parenthetical statement in Example 5 is the ***only*** basis for Vysis' contention that specific amplification is disclosed anywhere in the specification. However, The specification (and the inventors) clearly characterize Example 5 and Figure 5 as describing only non-specific amplification. Therefore, the '338 patent does not describe, either in Example 5 or anywhere else, methods that combine target capture with specific amplification. The patent claims cannot literally encompass methods that are not described in the specification as part of the invention made by the inventors.

III. TESTIMONY FROM KEY WITNESSES CLEARLY ESTABLISHES THE SCOPE OF THE INVENTION DISCLOSED IN THE '338 PATENT

In deposition, inventor Jon Lawrie clearly testified that his invention did not include methods of specific amplification such as PCR. Dr. Lawrie explained that the inventors were seeking *alternatives* to PCR. (Gen-Probe Memorandum at 20-21.)

Seeking to distance itself from its own inventor, Vysis argues that inventor Lawrie's subjective intent "is simply irrelevant to the claim construction issue." (Vysis Opp. Memo. at 14:11.) However, the interpretation to be given a term in a patent claim can *only* be determined and confirmed with a full understanding of what the inventors actually invented and intended to include within the claim. *Wang Laboratories, Inc. v. America Online, Inc.,* 197 F.3d 1377, 1384 (Fed. Cir. 1999); *Renishaw PLC v. Marposs Societa' Per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). It is inappropriate to disregard relevant evidence on any issue in any case, patent cases included. *Netword LLC v. Centraal Corp.*, 242 F.3d 1347, 1355 (Fed. Cir. 2001); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). The testimony of inventors is expressly recognized to be of value to the court in the claim construction process. *Voice Technologies Group, Inc. v. VMC Systems, Inc.*, 164 F.3d 605, 616 (Fed. Cir. 1999) (holding that the district court erred by excluding a deposition and video demonstration by the patent's inventor); *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479-80 (Fed. Cir.1998); *Evans Medical Ltd. v.*

American Cyanamid Co., 11 F. Supp.2d 338, 350-51 (S.D.N.Y. 1998), *aff'd without op.*, 215 F.3d 1347 (Fed. Cir. 1999) (claim construction based on intrinsic evidence was supported by the testimony of the inventor "against his own interest," which is "the best and most reliable extrinsic evidence").

What *is* forbidden is permitting the inventors to seek to *expand* the scope of patent claims, by testimony as to their subjective intent, over the description set forth in the specification. *See Markman*, 52 F.3d at 985. Dr. Lawrie's testimony about the actual invention does not expand the scope of the patent - his testimony aids in determining the actual scope of the invention and in limiting the scope of the patent in the face of Vysis' current effort to retroactively expand it.

Subsequent depositions of other inventors confirm that the invention described in the '338 patent does not include the combination of target capture with specific amplification. For example, Walter King was deposed on April 17, 2001. (Dr. King is the only one of the inventors still employed by Vysis.) Dr. King testified that that the invention claimed in the patent was conceived at a single meeting of the inventors in 1986 and he further testified that specific amplification was not discussed at that meeting:

> Q. You didn't talk about target capture and specific amplification in your meeting in 1986, correct? That's still your testimony?
>
> A. Yes.
>
> . . .
>
> Q. You didn't have any further involvement with respect to any of the work that related to this patent application until you signed the oath in December of 1997 [sic: 1987], correct?
>
> A. Yes.

(King Depo. at 184:1-16 (Exhibit 17).)

Dr. King also confirmed that the reason specific amplification methods such as PCR were not discussed at the meeting was that the inventors were trying to find ways *to get around* PCR. (King Depo at 185:23 - 186:6.) In his deposition testimony, Dr. King repeatedly stated the inventors' purpose:

///

Q From a high level perspective, what were the discussion topics addressed during this meeting?

A. I think that at the highest level we were looking for amplification methods ***that did not involve PCR amplification***.

(King Depo. at 45:10-15 (Exhibit 17) (emphasis added).)

Q. Okay. So the purpose - the general purpose of the discussion as I understand it that took place at Gene-Trak among the four doctors was to identify - in general identify an amplification technique that would amplify low concentrations of target nucleic acids in a sample, correct?

A. Yes.

Q. And as I understand your testimony, you wanted to find a technique ***that was different from PCR***, correct?

A. Yes.

(King Depo. at 47:9-20 (Exhibit 17) (emphasis added).)

When Dr. King he signed the oath in support of the patent application, he did not understand that the inventors claimed as their invention the combination of target capture and specific amplification:

Q. Okay. At the time that the four of you participated in the filing of the original application that led to the issuance of -- that disclosed amplification techniques that led to the issuance of the '338 patent, did you intend to claim the combination of target capture with PCR?

A. ***I don't have any recollection of that being tied together with PCR.***

(King Depo. at 136:14-21 (Exhibit 17) (emphasis added).)

Q. Did you believe that you had come up with the idea of combining target capture with PCR at any time in the work that was associated with the 338 patent?

A. ***Not specifically with PCR, no.***

Q. Did any of the other three identified inventors: Drs. Lawrie, Halbert or Collins ever indicate to you that - at any point in time, that they ever believed that one of them had come up with the idea of combining target capture with PCR?

A. No, I don't recall.

(King Depo. at 1339:21 - 140:7 (Exhibit 17) (emphasis added).)

Vysis also argues that Dr. Lawrie testified "that he believed that the invention of the '338 patent is not limited to nonspecific amplification." (Vysis Opp. Memo. at 14:14-15.) The question asked by Vysis' counsel concerned the patent application, *not* the invention itself. (Exhibit H.) But the inventors' testimony is relevant only to show what their actual *invention* was, not what they think the *patent application* disclosed. Testimony from the inventors about the patent application that seeks to expand what they actually invented is exactly the type of inventor testimony that is irrelevant to the claim construction process. *See Markman*, 52 F.3d at 985. The inventors' current understanding of the *patent* is irrelevant. Interpretation of the patent is an issue of law for the court. What matters is the inventors' understanding of what they actually invented, and on that issue it is clear they believe they invented the combination of target capture and *non-specific* amplification.

The best evidence on the question of how a person skilled in the art understood the invention of the '338 patent at the time the first application for the patent was filed is set forth in the December 1989 description of the invention by Dr. James Richards:

> Cetus, Sibia/Salk, Biotechnica, etc. all claim **specific** primers for amplification whereas the present invention claims uses of the opposite, namely, **non-specific** primer or promoters. . . .

(Exhibit 1, emphasis added.) Dr. Richards was clearly a person skilled in the art of nucleic acid hybridization as of December 1989. All witnesses in the case agree that Dr. Richards was knowledgeable with respect to both nucleic acid hybridization and the technologies available to Gene-Trak. (Smith Depo. at 21:12 - 22:9 (Exhibit 14); Ward Depo at 15:25 - 16:15 (Exhibit 15); Janiuk Depo. at 26:22 – 27:24 (Exhibit 13).) Dr. Richards' December 1989 analysis was made pre-litigation, when he had no motivation to do anything other than use his considerable education and experience, including discussions with the inventors and with patent counsel, to accurately describe the invention.

Vysis challenges Dr. Richards' statements on the ground that when he made them "he had not even read the patent application." However, on November 14, 1989, only a month before Dr. Richards recorded his analysis of the pending patent application, he requested a copy of the

application for review and it was sent to him by Gene-Trak's patent counsel. (Nov. 14, 1989 Letter (Exhibit 11); Janiuk Depo. at 56-57 (Exhibit 13).) At the time of his deposition, Dr. Richards could not *recall* having read the patent application twelve years earlier, but the application was sent to him in November 1989 and his December 1989 letter demonstrates his familiarity with the pending application[4].

Vysis also challenges the import of Dr. Richards' statements on the grounds that he only "worked in business development." (Vysis Opp. Memo at 14:20.) However, this mischaracterization of Dr. Richards' education, experience and responsibilities is unwarranted[5].

IV. NOTHING IN THE PROSECUTION HISTORY EXPANDS THE SCOPE OF THE INVENTION

As discussed above, the '338 patent teaches that a target capture step improves non-specific amplification. The patent describes only non-specific amplification methods. The patent does *not* refer to specific amplification and does not teach any benefits from the combination of target capture and specific amplification. The inventors have admitted they did not invent a method that combines target capture with specific amplification, and Dr. Richards' letter confirms that one skilled in the art did not understand the invention to encompass specific amplification.

Faced with this overwhelming evidence, Vysis contends that the "prosecution history" shows that the invention includes specific amplification. However, in this case the prosecution history for the '338 patent does not add anything to the claim construction process.

For purposes of claim construction, the patent's claims, specification, and prosecution history are considered to be "intrinsic evidence." Within this intrinsic evidence, "there is a hierarchy of analytical tools." *Digital Biometrics Inc. v. Identix Inc.*, 149 F.3d 1335, 1344 (Fed.

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[4] Moreover, if Dr. Richards did not read the application, his only other sources of information were very reliable ones -- inventor Jon Lawrie and Gene-Trak's patent counsel, Tony Janiuk. (Richards Depo. at 152:5-13; 186:11-21 (Exhibit 10.)

[5] Dr. Richards received a Ph.D. in Microbiology and Biochemistry from Southern Illinois University. (Richards Depo., Exh. 10, at 7:17-20.) He managed Gene-Trak's technology assets and technology needs. (*Id.* at 44:18 - 45:9; 47:22 - 48:24.) He was a member of the Gene-Trak patent committee and discussed patents with Gene-Trak's patent counsel. (*Id.* at 150:15-21.) When presentations on patent matters, including target capture patents, were made to the Gene-Trak partnership committee and to the Gene-Trak scientific advisory board, Dr. Richards made those presentations. (*Id.* at 60:8-13; 82:3-6; 150:9-14; 151:1-4.)

Cir. 1998). *Accord, Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The sources are considered, in descending order of weight and importance: (1) the claim language itself; (2) the specification of the patent; and (3) the prosecution history. *Digital Biometrics, supra*, 149 F.3d at 1344. *See also McKinley v. Franklin Sports, Inc.*, 45 F.Supp.2d 1141, 1143 (prosecution history is "tertiary" consideration).

As recognized in *Vitronics Corp.*, the patent specification "usually . . . is dispositive." *Vitronics*, 90 F.3d at 1582. The prosecution history cannot expand what was originally disclosed in the "written description" of the invention set forth in the specification, and claims may not be interpreted to be broader than what was described in the specification.[6] When the specification establishes the meaning for a term without ambiguity or incompleteness, there is no need to search further for the meaning of the term. *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1472, 1478 (Fed. Cir. 1998).

Although Vysis urges the court to consider the prosecution history, it does not provide any guidelines about *how* the prosecution history is properly used in claim construction. In fact, prosecution history is relevant to claim construction when the patent applicant, in the course of patent prosecution, agreed to limit the scope of its claims or disclaim certain subject matter in order to obtain allowance of the patent. "The prosecution history *limits* the interpretation of claim terms so as to exclude any interpretation that was *disclaimed* during prosecution[7]." *Southwall Technologies, Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1579 (Fed. Cir. 1995), *cert. denied*, 516 U.S.

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[6] In particular cases prosecution history may add nothing to the claim construction process. *See, e.g., SciMed Life Systems, Inc. v. Advanced Cardiovascular Systems, Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001)("There is nothing pertinent to this issue [of claim construction] in the prosecution history"); *Mantech Environmental Corp. v. Hudson Environmental Services Inc.*, 152 F.3d 1368, 1370 n.6, 1374 n.10 (Fed. Cir. 1998) ("There is no relevant prosecution history"). In this case the specification clearly establishes the scope of the invention. The prosecution history does not contribute to claim interpretation.

[7] In practice, there is no meaningful distinction between the use of prosecution history in claim interpretation and the operation of "prosecution history estoppel." *HBB Limited Partnership v. Ford Motor Co.*, 1996 U.S. Dist. Lexis 4047 at 19-20 (N.D. Ill. 1996); *Abtox, Inc. v. Exitron Corp.*, 899 F.Supp. 775, 781 (D. Mass 1995). *See also McGill Inc. v. John Zink Co.*, 736 F.2d 666, 673 (Fed. Cir. 1984). Both applications of the prosecution history are triggered by concessions made in order to obtain the patent. *HBB Limited Partnership v. Ford Motor Co.*, 1996 U.S. Dist. Lexis 4047 at 20 (N.D. Ill. 1996).

987 (1995)(emphasis added)[8]. Therefore, "The prosecution history is, in most instances, cited *against* a broad interpretation later asserted by the patent owner," 5A Chisum on Patents, Interpretation of Claims, § 18.03[d] at 18-117 (2000), because "the patentee has disclaimed or disavowed a certain scope or definition for the purpose of escaping rejection by the PTO." *McNeil-PPC, Inc. v. Bayer Corp.*, 2000 U.S. Dist. Lexis 16431 at 16 (E.D. Pa. 2000).

In this case, Vysis does not and cannot cite any action which it took to narrow the claims and specification in order to avoid prior art references and obtain allowance of the patent. There is simply nothing in the prosecution history that is cognizable in the claim construction process in this court.

Instead of citing relevant prosecution history in accordance with the rules established by applicable precedent, Vysis seeks to stand the rules of construction on their head and *expand* the written description of the invention set forth in the specification based simply on argument of counsel in the course of patent prosecution. Self-serving statements of Vysis' patent counsel, which were made late in the course of patent prosecution in an effort to expand the original specification based on post-filing developments, are not "prosecution history" for purposes of claim construction. Such belated argument of counsel cannot expand the scope of the invention as described in the patent application. The written description requirement of 35 U.S.C. § 112 preempts any such "bootstrapping" use of the prosecution history. An inventor may not define claim terms more broadly during prosecution, to cover developments that took place after the patent application was filed, than those terms were defined in the patent application. *Schering Corp. v. Amgen, Inc.*, 18 F. Supp. 372, 389-90, (D. Del. 1998), *aff'd*, 222 F.3d 1347, (Fed. Cir. 2000).

Vysis' attempt to rely on its patent counsel's arguments in the course of patent prosecution must also fail because they were made *too late in time* to be relevant. In the claim construction process, the Court seeks to determine how a person skilled in the art would have understood the

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[8] *Accord, Graham v. John Deere Co.*, 383 U.S. 1 (1966): *Spectrum International, Inc. v. Sterlite Corp.*, 164 F.3d 1372, 1378-79 (Fed. Cir. 1998); *Zenith Lab., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1421 (Fed. Cir.), *cert. denied*, 513 U.S. 995 (1994); *Standard Oil Co. v. American Cyanmid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985).

invention described in the patent as of the date of the first relevant patent application. *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998); *Markman, supra,* 52 F.3d at 985-986. Here, that date is December 21, 1987. ('338 patent at 1, (Exhibit 8); May 24, 2001 Banks Decl., ¶ 3.) Prosecution history may be an important source of intrinsic evidence in interpreting claims *if* it contains *contemporaneous* exchanges between the applicant and the patent examiner. *Desper Products Inc. v. QSound Labs Inc.*, 157 F.3d 1325, 1336 (Fed. Cir. 1998); *Digital Biometrics Inc. v. Identix Inc.*, 149 F.3d 1335, 1344 (Fed. Cir. 1998). However, courts must be skeptical when papers filed with the PTO years after an initial patent application are offered to prove the understanding of those skilled in the art at the time the application was filed. *See Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1328 (Fed. Cir. 2000) (court could not consider amended patent claims that did not appear in original application to show that inventor was in possession of the invention subsequently claimed at the time original application was filed).

Vysis' first contention that its invention encompassed specific amplification methods such as PCR was not made until December 1995, *eight years after its first patent application was filed*.[9] This contention was first made in support of Vysis' *fourth* application[10] for a patent on the invention at issue. (Vysis Ex. E.) Eight years and four applications after its first filing, Vysis drew a new patent examiner and argued for the first time that the invention was an *improvement to PCR*. This contention, made only in the form of argument of counsel during patent prosecution, is completely unsupported by the patent application, which contains no mention whatsoever of PCR.

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[9] In its brief, Vysis describes its initial argument as to PCR as having been set forth in a paper filed with the PTO "responding to November 5, 1992 Office Action." (Opp. Memo. at 5:17-18. By this citation, Vysis attempts to hide the actual date of its argument to the PTO -- **December 5, 1995** -- almost 8 years after the first patent application was filed and three years after the PTO Office Action to which it purported to respond. (Vysis Exhibit E.)

[10] Vysis did not respond to the PTO's November 1992 office action. As a result, its patent application was abandoned as of February 5, 1993. (Exhibit 19.)

Vysis did not take any further steps to seek a patent for the invention until May 3, 1994, more than one year after it abandoned the application, when Vysis petitioned the PTO to "revive" the patent application. (Gen-Probe Exhibit 20.) That petition was denied by the PTO on the ground Vysis had waited more than one year after abandonment to seek revival. (Gen-Probe Exhibit 21.) In May 1994, Vysis filed a *fourth* application, an identical copy of the three prior applications. Vysis made its first arguments addressed to PCR in support of this fourth application. (The relevant facts pertaining to the prosecution are set forth in the Reply Declaration of Christine Gritzmacher submitted concurrently herewith.)

The inventors never represented to the PTO under oath that their invention encompassed PCR.

The prosecution history arguments cited by Vysis are irrelevant because they are simply the argument of counsel, first made in December 1995, more than 8 years after the invention is alleged to have been made. Vysis' belated prosecution arguments cannot retroactively change the patent specification, nor are they evidence of the understanding of persons skilled in the art as of December 21, 1987.

The argument of counsel is not made more significant because it was successful in persuading the PTO to modify the PTO's views of the patent's subject matter. The PTO employs a very different mode of claim construction than is to be applied in litigation. *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989). During prosecution in the PTO, the claims are interpreted as broadly as possible and there the limitations of the specification are not read into the claims. *Id.* at 322. *Accord, In re Morris*, 127 F.3d 1048, 1053-54 (Fed. Cir. 1997). In this Court, however, claims are to be interpreted narrowly based on the disclosures of the specification. *Wang Laboratories, Inc. v. America Online, Inc.*, 197 F.3d 1377, 1384 (Fed. Cir. 1999).

Second, the PTO's comments on the nature of the invention receive no deference in this Court. Claim construction is a pure question of law, even when it encompasses subsidiary factual issues. *Cybor Corp. v. FAS Tech., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998) (*en banc*). Claim interpretations are subject to de novo review, without deference to factual findings. *Id.* Deference may certainly not be given to a PTO examiner's decision in the course of an *ex parte* proceeding. *See id.; see also Quad Environmental Tech v. Union Sanitary Dist.*, 946 F.2d 870, 876 (Fed. Cir. 1991) (Patent validity issues are "ultimately for the courts to decide, without deference to the ruling of the patent examiner.")

Third, where an examiner's statements, made in the course of an *ex parte* PTO proceeding, are not persuasive in light of all the evidence before a court, the court should disregard the examiner's statements, particularly when the court has received, in an adversary hearing, evidence which was not before the patent examiner[11]. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320,

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[11] Here, the patent examiner did not have access to the inventor testimony, the Richards letter, or other relevant evidence, because Vysis did not submit such evidence and the *ex parte* nature of the

1329 (Fed. Cir. 2000). *See also Eastman Kodak Co. v. Goodyear Tire & Rubber Co.*, 114 F.3d 1547, 1556 (Fed. Cir. 1997), abrogated on other grounds (standard of appellate review), *Cybor*, 138 F.3d at 1456.

Vysis' final prosecution history argument, that the PTO's rejection of the initial applications as "obvious" in light of the PCR patent, does not in any way support the proposition that the '338 patent encompasses PCR. In response to the invention of PCR, and in an effort to engineer around it, Vysis sought to develop methods that used non-specific amplification with an initial target capture step. Vysis sought to achieve target specificity by target capture rather than by specific amplification primers. Inventor Lawrie himself was concerned that this use of specific capture and non-specific amplification was "too close" to the PCR method invented by Kary Mullis and others at Cetus Corp. (Lawrie Notes (Exhibit 12); Lawrie Depo. at 102:15-20 (Exhibit 16.) Vysis' initial applications were not rejected by the PTO because Vysis' claims encompassed PCR, but because those claims were an "obvious" attempt to achieve the same result as PCR in a different manner.

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PTO proceedings precluded any other party from participating. Vysis did not provide the patent examiner in the original prosecution with any evidence that the inventors agreed that the invention encompassed specific amplification. Nor has Vysis provided such evidence to the examiner in the pending reissue proceeding. Vysis has relied solely on argument of counsel and has not submitted depositions, declarations, or evidentiary documents.

V. CONCLUSION

The '338 patent describes and encompasses only methods of non-specific amplification. Gen-Probe's products do not incorporate non-specific amplification and the Motion for Partial Summary Judgment should be granted.

Dated: June 1, 2001

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J. CHRISTOPHER JACZKO
COOLEY GODWARD LLP

DOUGLAS E. OLSON
BROBECK PHLEGER & HARRISON LLP

R. WILLIAM BOWEN, JR.
GEN-PROBE INCORPORATED

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Attorneys for Plaintiff
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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99CV2668 H (AJB)

PLAINTIFF GEN-PROBE INCORPORATED'S PROOF OF SERVICE

Date: June 8, 2001
Time: 10:30 a.m.
Dept: Courtroom 1

PROOF OF SERVICE
(FRCP 5)

I am a citizen of the United States and a resident of the State of California. I am employed in San Diego, State of California, in the office of a member of the bar of this Court, at whose direction the service was made. I am over the age of eighteen years, and not a party to the within action. My business address is 4365 Executive Drive, Suite 1100, San Diego, California 92121-2128. On the date set forth below I served the documents described below in the manner described below:

1. PLAINTIFF GEN-PROBE INCORPORATED'S REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT
2. REPLY DECLARATION OF CHRISTINE GRITZMACHER IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT
3. REPLY DECLARATION OF STEPHEN P. SWINTON IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT
4. REPLY DECLARATION OF DR. JOSEPH O. FALKINHAM IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT
5. REPLY DECLARATION OF R. WILLIAM BOWEN IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT
6. REPLY NOTICE OF LODGMENT OF EXHIBITS IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT
7. STIPULATION AND [PROPOSED] ORDER ALLOWING GEN-PROBE INCORPORATED TO FILE UNDER SEAL CERTAIN DOCUMENTS UPON WHICH IT RELIES TO SUPPORT ITS REPLY RE MOTION FOR PARTIAL SUMMARY JUDGMENT

☐ (BY U.S. MAIL) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of correspondence for mailing with the United States Postal Service, and I caused such envelope(s) with postage thereon fully prepaid to be placed in the United States Postal Service at Palo Alto, California.

☐ (BY MESSENGER SERVICE) by consigning the document(s) to an authorized courier and/or process server for hand delivery on this date. See attached Proof of Personal Service.

☑ (BY FACSIMILE) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of document(s) to be transmitted by facsimile and I caused such document(s) on this date to be

transmitted by facsimile to the offices of addressee(s) at the numbers listed below.

☑ (BY OVERNIGHT MAIL) I am personally and readily familiar with the business practice of Cooley Godward llp for collection and processing of correspondence for overnight delivery, and I caused such document(s) described herein to be deposited for delivery to a facility regularly maintained by Federal Express for overnight delivery.

4106 2110 3579

on the following part(ies) in this action:

Thomas W. Banks Esq.
Finnegan, Henderson, Farabow, et al.
700 Hansen Way
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Tel: (650) 849-6600
Fax: (650) 849-6666
Attorneys for Vysis, Inc.

Executed on June 1, 2001, at San Diego, California.

Liz Hoke

PROOF OF PERSONAL SERVICE

I hereby declare:

I am employed in the City of San Diego, County of San Diego, California; I am over the age of eighteen years and not a party to the within cause; my business address is Knox Attorney Service, 2250 Fourth Avenue, San Diego, California 92103.

On June 1, 2001, I served the within document(s):

1. PLAINTIFF GEN-PROBE INCORPORATED'S REPLY MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT
2. REPLY DECLARATION OF CHRISTINE GRITZMACHER IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT
3. REPLY DECLARATION OF STEPHEN P. SWINTON IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT
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7. STIPULATION AND [PROPOSED] ORDER ALLOWING GEN-PROBE INCORPORATED TO FILE UNDER SEAL CERTAIN DOCUMENTS UPON WHICH IT RELIES TO SUPPORT ITS REPLY RE MOTION FOR PARTIAL SUMMARY JUDGMENT

on the interested parties in this action by personally hand delivering a copy of said document(s) to the address(es) listed below:

John H. L'Estrange, Jr. Esq.
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Attorneys for Vysis, Inc.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct, and that this declaration was executed on June 1, 2001.

SIGNATURE: _____

PRINT NAME: _____

CONFIRMATION REPORT - MEMORY SEND

Time : JUN-01-01 13:00
Fax number:
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Job	:	590
Date	:	JUN-01 12:48
To	:	16508496666#
Doc. pages	:	52
Start time	:	JUN-01 12:48
End time	:	JUN-01 13:00
Pages sent	:	52
Job:590		*** SEND SUCCESSFUL ***

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DATE: June 1, 2001

PLEASE DELIVER TO:	PHONE NO.	FAX NO.
Thomas W. Banks Finnegan Henderson Farabow	650 849 6600	650 849 6666

FROM: J. Christopher Jaczko PHONE: (858) 550-6027 REPLY FAX: (858) 453-3555

RE: Gen-Probe, Inc. v. Vysis, Inc.

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99cv2668 H (AJB)

REPLY NOTICE OF LODGMENT IN SUPPORT OF PLAINTIFF GEN-PROBE INCORPORATED'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept: Courtroom 1

TO ALL PARTIES AND THEIR ATTORNEYS OF RECORD:

PLEASE TAKE NOTICE that Plaintiff Gen-Probe Incorporated hereby lodges the following exhibits in support of Gen-Probe Incorporated's Motion for Partial Summary Judgment:

EXHIBIT 11: A true and correct copy of a letter dated November 14, 1989 from Anthony J. Janiuk to Dr. James C. Richards.

EXHIBIT 12: A true and correct copy of handwritten notes made by Jonathon Laurie, Ph.D.

EXHIBIT 13: A true and correct copy of portions of the transcript of the deposition of Anthony J. Janiuk taken May 16, 2001. **[Filed Under Seal]**

EXHIBIT 14: A true and correct copy of portions of the transcript of the deposition of Alan E. Smith, Ph.D., taken May 17, 2001.

EXHIBIT 15: A true and correct copy of portions of the preliminary or "rough" transcript of the deposition of David Ward, Ph.D., taken May 18, 2001. **[Filed Under Seal]**

EXHIBIT 16: A true and correct copy of portions of the transcript of the deposition of Jon Laurie, Ph.D., taken February 15, 2001. **[Filed Under Seal]**

EXHIBIT 17: A true and correct copy of portions of the transcript of the deposition of Walter King, Ph.D., taken April 18, 2001. **[Filed Under Seal]**

EXHIBIT 18: A true and correct copy of portions of the transcript of the deposition of Donald Neil Halbert, Ph.D., taken April 19, 2001. **[Filed Under Seal]**

EXHIBIT 19: A true and correct copy of the Patent & Trademark Office's Notice of Abandonment of U.S. Patent application no. 07/944,505, dated June 16, 1993.

EXHIBIT 20: A true and correct copy of the Petition to Revive the [07/944,505] Application as Unintentionally Abandoned, dated May 3, 1994.

EXHIBIT 21: A true and correct copy of the Patent & Trademark Office's notice of denial of petition to revive [07/944,505] application, dated October 27, 1994.

EXHIBIT 22: Summary of prosecution history of United States Patent No. 5,750,338.

Dated: June 1, 2001

STEPHEN P. SWINTON
J. CHRISTOPHER JACZKO
COOLEY GODWARD LLP

DOUGLAS E. OLSON
BROBECK PHLEGER & HARRISON LLP

R. WILLIAM BOWEN, JR.
GEN-PROBE INCORPORATED

By: _____
J. Christopher Jaczko

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312-856-7972
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Anthony J. Janiuk
Patent Attorney

November 14, 1989

Dr. James C. Richards
Gene-Trak Systems
31 New York Avenue
Framingham, Massachusetts 01701

Dear Dr. Richards:

Application: Target and Background Capture Methods With Amplification for Affinity
Inventors: Mark L. Collins; Donald N. Halbert Walter King and Jonathan M. Lawrie
Our Case No: 25,83501
U.S. Serial No. 139,920

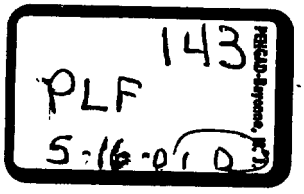
Per your request enclosed please find an application copy of the above identified patent application.

Very truly yours,

Anthony J. Janiuk

Anthony J. Janiuk
Mail Code 1907

AJJ:vay



copy of application Del. Power of Atty
+ drawings Declar

EXH 11 PAGE 3

143

Sep 14 '95 09:59 P.02

(4) Specific Capture
Non-specific amplification
Specific Capture
too close to CETUS?

hexamer priming
DNA polymerase

denature, repetitive polymerase

recapture products
& probe

EXHIBIT 13

Exhibit 13 Filed Under Seal

VOL. I, PAGES 1 - 66

UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

CIVIL ACTION NO. 99CV2668 H (AJB)

GEN-PROBE, INCORPORATED

Plaintiff

v.

VYSIS, INC.

Defendant

- - - - - - - - -

Deposition of Alan E. Smith, Ph.D.

Thursday, May 17, 2001

Genzyme Corporation

One Kendall Square

Cambridge, Massachusetts

- - - - - - - - -

Reporter: Deborah Roth, RPR

A. I don't specifically recall seeing it before.

Q. Did you generally receive, either prior to or at the meeting of the management committee or the partnership committee, a copy of an agenda?

A. I don't recall.

Q. On the first page of Exhibit 53 there's a list of topics and Topic No. 7 is patent strategy, with a presentation to be made by Dr. James Richards. Do you see that?

A. Yes.

Q. Can you recall Dr. Richards giving presentations on patents to the management committee or the partnership committee of Gene-Trak?

A. Do I remember generally? Generally, yes.

Q. Do you remember that Dr. Richards was Gene-Trak's director of business development and licensing?

A. Yes.

Q. Did Dr. Richards, when he made presentations on patents to the partnership committee, appear knowledgeable with respect to the technology he discussed?

A. Did he appear knowledgeable? I think the

02:36 1 answer is yes.
02:36 2 Q. I'm sorry?
02:37 3 A. He appeared knowledgeable. My recollection
02:40 4 is that he appeared knowledgeable.
02:42 5 Q. Did he seem to have an understanding of
02:45 6 nucleic acid hybridization technologies, to you?
02:48 7 A. To me at the time?
02:49 8 Q. Yes.
02:50 9 A. Yes.
03:04 10 Q. I would like you to look at what has been
03:07 11 previously marked as Exhibit 56, which appears to be
03:12 12 an agenda for a partnership committee meeting on
03:14 13 June 11, 1987.
03:17 14 Would you look at that agenda so that
03:20 15 you can tell me whether or not you've seen it
03:23 16 before.
04:04 17 A. I don't specifically remember seeing this
04:06 18 before.
04:09 19 Q. Do you think it's likely that you received a
04:11 20 copy of Exhibit 56 in June 1987?
04:15 21 MR. LIPSEY: I object to the form.
04:19 22 A. I don't recall.
04:23 23 Q. I would like you to look on the first page
04:25 24 of Exhibit 56. Topic 3 under the sub-heading

Exhibit 15 Filed Under Seal

Exhibit 16 Filed Under Seal

09533906.021202

Exhibit 17 Filed Under Seal

Exhibit 18 Filed Under Seal

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
07/944,505	09/14/92	COLLINS	M 25,835-06

18N1/0616

THOMAS W. TOLPIN
AMOCO CORPORATION
55 SHUMAN BOULEVARD, SUITE 600
NAPERVILLE, IL 60563-8487

CHAMBER EXAMINER	
ART UNIT	PAPER NUMBER
1807	5

DATE MAILED: 06/16/93

NOTICE OF ABANDONMENT

This application is abandoned in view of:

1. ☐ Applicant's failure to respond to the Office letter, mailed 11/5/92.
2. ☐ Applicant's letter of express abandonment which is in compliance with 37 C.F.R. 1.138.
3. ☐ Applicant's failure to timely file the response received _____ within the period set in the Office letter.
4. ☐ Applicant's failure to pay the required issue fee within the statutory period of 3 months from the mailing date of _____ of the Notice of Allowance.
   ☐ The issue fee was received on _____.
   ☐ The issue fee has not been received in Allowed Files Branch as of _____.

   In accordance with 35 U.S.C. 151, and under the provisions of 37 C.F.R. 1.316(b), applicant(s) may petition the Commissioner to accept the delayed payment of the issue fee if the delay in payment was unavoidable. The petition must be accompanied by the issue fee, unless it has been previously submitted, in the amount specified by 37 C.F.R. 1.17 (l), and a verified showing as to the causes of the delay.

   If applicant(s) never received the Notice of Allowance, a petition for a new Notice of Allowance and withdrawal of the holding of abandonment may be appropriate in view of Delgar Inc. v. Schuyler, 172 U.S.P.Q. 513.
5. ☐ Applicant's failure to timely correct the drawings and/or submit new or substitute formal drawings by _____ as required in the last Office action.
   ☐ The corrected and/or substitute drawings were received on _____.
6. ☐ The reason(s) below.

MARGARET MOSKOWITZ
SUPERVISORY PATENT EXAMINER
GROUP 180

PTO-1432 (REV 5-83)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Mark L. Collins, et al.	)	
		)	Group Art Unit: 1807
SERIAL NO:	07/944,505	)	
		)	Examiner: S. Chambers
FILED:	September 14, 1992	)	
		)	
FOR:	TARGET AND BACKGROUND CAPTURE METHODS WITH AMPLIFICATION FOR AFFINITY ASSAYS	)	Docket: 2583506

PETITION TO REVIVE THE APPLICATION AS UNINTENTIONALLY ABANDONED

Hon. Commissioner of Patents
And Trademarks
Washington, D.C. 20231

Sir:

Applicants respectfully petition for revival of the above-captioned application under 37 CFR §1.137(b) as unintentionally abandoned. The application stands abandoned at this time as a result of Applicants' failure to respond to an Office letter mailed November 5, 1992. The abandonment occurred as a result of the oversight of Applicants' representative and was not intended by Applicants. Applicants did not become aware of the abandonment until advised of such by an Office letter mailed June 16, 1993.

Applicants' petition for revival must be accompanied by the appropriate fee as provided by 37 CFR §1.17(m) and a proposed response to the Office letter mailed November 5, 1992. The fee prescribed by 37 CFR §1.17(m) is enclosed herewith. The required response is provided by refiling the application concurrently with this Petition.

Applicants submit their petition is proper and respectfully request that their petition be granted.

Respectfully submitted,

May 3, 1994

Norval B. Galloway

Norval B. Galloway
Registration No. 33,595
Amoco Corporation
55 Shuman Blvd.
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Naperville, IL 60563
(708) 717-2447

"Express Mail" mailing label number TB283682TX
Date of Deposit May 3, 1994

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231

Anna Franz
5-3-94

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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

MEM/JVN/mm.10

Paper No. 7

Thomas W. Tolpin
Amoco Corporation
55 Shuman Boulevard
Suite 600
Naperville, IL 60563-8487

In re Application of
Mark L. Collins, et al.
Serial No. 07/944,505
Filed: September 14, 1992
Attorney Docket No. 25.835-06

ON PETITION

This is a decision on the petition under 37 CFR 1.137(b), filed October 24, 1994, to revive the above-identified application.

This application became abandoned for failure to respond in a timely manner to the final Office action of November 5, 1992 which set a shortened statutory period for response of three months. Therefore, the application became abandoned on February 6, 1993.

Since this petition was filed more than one year after the date on which the application became abandoned, the petition is barred; 37 CFR 1.137(b).

In view of the above, the present petition is dismissed as moot. Therefore, the petition fee of $1,170 has not been charged to petitioner's Deposit Account.

Petitioner may have relief under the provisions of 37 CFR 1.137(a). However, in view of the fact that this case has been abandoned for an inordinate period of time, petitioner must show diligence between the time of becoming aware of the abandonment of the above-identified application and the filing of a petition to revive. Note In re Application of S, 8 USPQ2d 1630.

Further correspondence with respect to this matter should be addressed as follows:

By mail: Commissioner of Patents and Trademarks
Box DAC
Washington, D.C. 20231

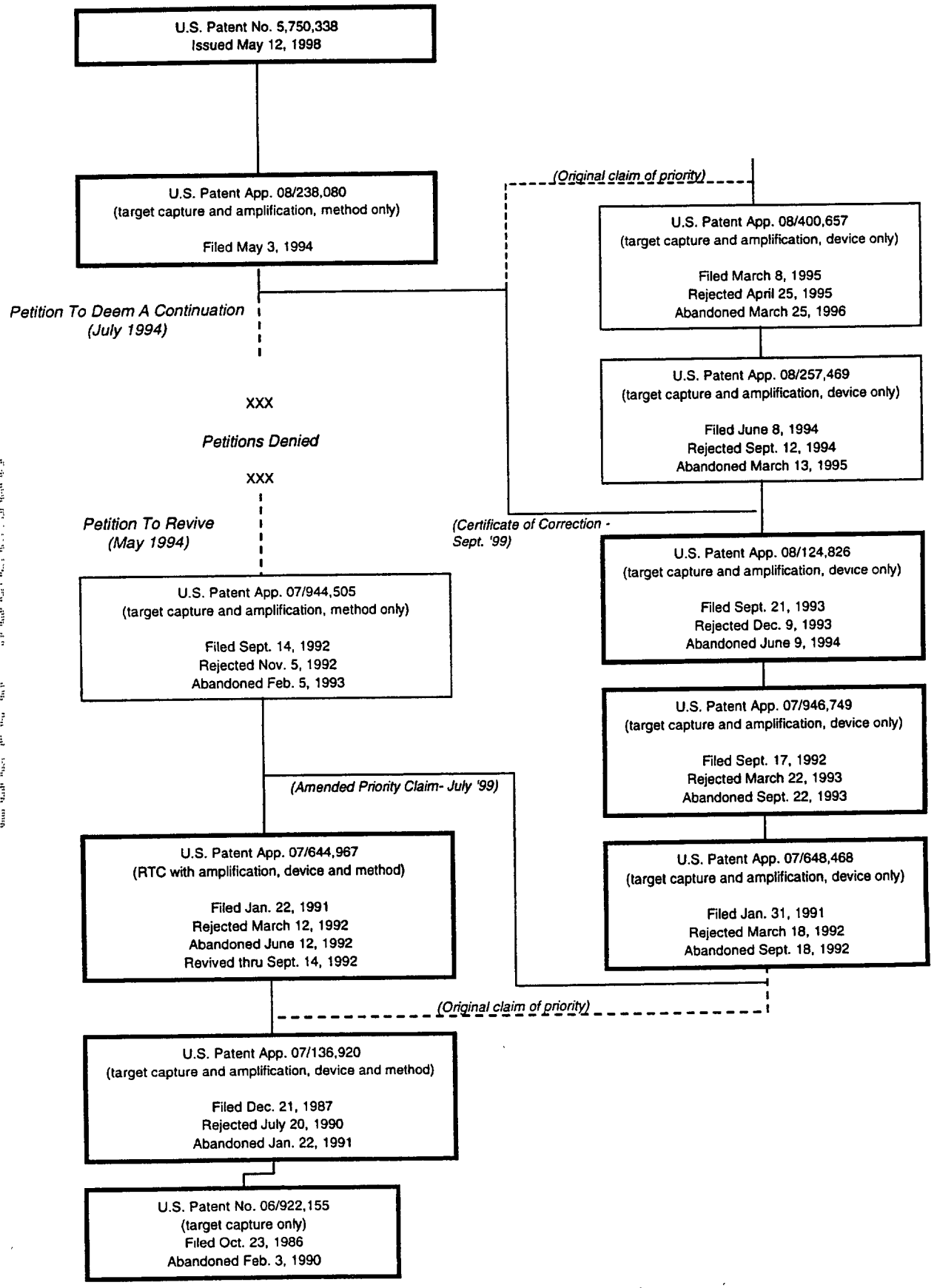
By FAX: (703) 308-6916
Attn: Office of Petitions

Telephone inquiries should be directed to the Office of Petitions Staff at (703) 305-9282.

Karen M. Babington
for Jeffrey V. Nase, Director
Office of Petitions
Office of the Assistant Commissioner
for Patents

0000000000

'338 PATENT HISTORY WITH POST-ISSUANCE CORRECTIONS AND AMENDMENTS



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4365 Executive Drive, Suite 1100
San Diego, California 92121-2128
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Facsimile: (858) 410-8637

Attorneys for Plaintiff
Gen-Probe Incorporated

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99-CV-2668H AJB
JUDGE MARILYN L. HUFF

REPLY DECLARATION OF STEPHEN P. SWINTON IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept: Courtroom 1

I, Stephen P. Swinton, declare as follows:

1. I am a member of the State Bar of California and admitted to practice before this Court. I am a partner with the law firm of Cooley Godward LLP and am one of the counsel of

record in this action for plaintiff Gen-Probe Incorporated.

2. I attended the deposition of Walter King, Ph.D., at Downers Grove, Illinois on April 18, 2001. I asked the questions and heard the responses given by Dr. Lawrie at the deposition. The deposition of Dr. King was stenographically recorded and transcribed. The excerpts of the Lawrie deposition set forth in Exhibit 17 to the accompanying Reply Notice of Lodgment are true and correct copies of the certified deposition transcript and accurately state the questions and answers at the King deposition.

3. I attended the deposition of Donald Neil Halbert, at Abbot, Illinois on April 19, 2001. I asked the questions and heard the responses given by Dr. Halbert at the deposition. The deposition of Dr. Halbert was stenographically recorded and transcribed. The excerpts of the Halbert deposition set forth in Exhibit 18 to the accompanying Reply Notice of Lodgment are true and correct copies of the certified deposition transcript and accurately state the questions and answers at the Halbert deposition.

I declare under penalty of perjury under the laws of the United States of America that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. This declaration was executed by me at San Diego, California on May 31, 2001.

Stephen P. Swinton

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED, Plaintiff, v. VYSIS, INC., Defendant.	No. 99CV2668 H (AJB) THE HONORABLE MARILYN L. HUFF **REPLY DECLARATION OF R. WILLIAM BOWEN IN SUPPORT OF GEN-PROBE'S MOTION FOR SUMMARY JUDGMENT** Date: June 8, 2001 Time: 10:30 a.m. Place: Courtroom 1

I, R. William Bowen, declare as follows:

1. I am a member of the State Bar of California and admitted to practice before this Court. I am one of the counsel of record in this action for plaintiff Gen-Probe Incorporated.

2. I attended the deposition of Anthony J. Janiuk, Esq. at Boston, Massachusetts on May 16, 2001. I asked the questions and heard the responses given by Mr. Janiuk at the deposition. The deposition of Mr. Janiuk was stenographically recorded and transcribed. The

excerpts of the Janiuk deposition set forth in Exhibit 13 to the accompanying reply notice of lodgment are true and correct copies of the certified deposition transcript and accurately state the questions and answers at the Janiuk deposition.

3. At the deposition of Mr. Janiuk, a letter dated November 14, 1989 from Mr. Janiuk to Dr. James Richards was marked as Plaintiff's Deposition Exhibit 143 and authenticated by the witness. A true and correct copy of this letter is attached as Exhibit 11 to the accompanying reply notice of lodgment.

4. I attended the deposition of Alan E. Smith, Ph.D., at Cambridge, Massachusetts on May 17, 2001. I asked the questions and heard the responses given by Dr. Smith at the deposition. The deposition of Dr. Smith was stenographically recorded and transcribed. The excerpts of the Smith deposition set forth in Exhibit 14 to the accompanying reply notice of lodgment are true and correct copies of the certified deposition transcript and accurately state the questions and answers at the Smith deposition.

5. I attended the deposition of David Ward, Ph.D., at New Haven, Connecticut on May 18, 2001. I asked the questions and heard the responses given by Dr. Ward at the deposition. The deposition of Dr. Ward was stenographically recorded and transcribed. The excerpts of the Ward deposition set forth in Exhibit 15 to the accompanying reply notice of lodgment are true and correct copies from the preliminary or "rough" deposition transcript and accurately state the questions and answers at the Ward deposition.

6. I attended the deposition of Jon Lawrie, Ph.D., at Raleigh - Durham, North Carolina on February 15, 2001. I asked the questions and heard the responses given by Dr. Lawrie at the deposition. The deposition of Dr. Lawrie was stenographically recorded and transcribed. The excerpts of the Lawrie deposition set forth in Exhibit 16 to the accompanying reply notice of lodgment are true and correct copies of the certified deposition transcript and accurately state the questions and answers at the Lawrie deposition.

7. At the deposition of Dr. Lawrie, a set of handwritten notes made by Dr. Lawrie was marked as Plaintiff's Deposition Exhibit 49 and authenticated by the witness. A true and correct copy of page these notes is attached as Exhibit 12 to the accompanying reply notice of lodgment.

I hereby declare under penalty of perjury that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Executed at San Diego, California on May 31, 2001.

R. William Bowen

R. William Bowen

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99-CV-2668H AJB
JUDGE MARILYN L. HUFF

REPLY DECLARATION OF DR. JOSEPH O. FALKINHAM IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

I, Joseph O. Falkinham, III, hereby declare as follows:

1. I have personal knowledge of the facts set forth below, and, if called as a witness in this action, I could and would testify competently to the truth thereof.

2. I have been retained as an expert witness in this lawsuit. I have reviewed the specification and claims of the '338 patent), as well as Vysis, Inc.'s Opposition to Gen-Probe's Motion for Summary Judgment and the Declaration of Dr. David H. Persing. I submit this declaration to rebut certain statements made by Dr. Persing.

SUMMARY OF OPINION

3. In paragraph 13 of his declaration, Dr. Persing states that he believes that Example 5 describes specific amplification because:

> "In particular, while Example 5 states initially that random oligohexamer primers can be used to achieve non-specific amplification, Example 5 also discloses that "[a]lternatively, the double stranded DNA can be formed by synthesis starting from capture probe a." Col. 31, lines 48-49. In this instance, the capture probe acts as the primer. Since the capture probe binds specifically to the target DNA, the capture probe would be a specific primer to the target. This is an example of specific amplification because the primer, capture probe a, binds to a specific, unique DNA sequence in the target organism."

4. I disagree with Dr. Persing's conclusion for the following reasons.

5. Example 5 of the '338 specification teaches only the combination of target capture with *non-specific* amplification. Example 5 is set forth in three paragraphs of text beginning at col. 31, line 24 of the '338 patent. The first paragraph consists of a single sentence that states that the example teaches non-specific amplification:

> In this example, both ***non-specific*** replication of target DNA and transcription of that DNA are used to amplify capture target DNA.

(Exh. 8, at col. 31, ll. 24-54, emphasis added.) The second paragraph of example 5 provides the details of a particular method, and teaches the use of *random* (e.g., non-specific) primers and non-specific transcription in the amplification process used in the method. (Exh. 8, at col. 31, ll. 31-33.) As a result of these explicit statements, it is my opinion that a person skilled in the art would understand that Example 5 discloses a non-specific method of amplification.

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6. This understanding is reinforced by the fact that Example 5 refers to and incorporates Figure 5 of the drawings included in the patent. (Exhibit 8 at col. 31, l. 28.) The drawings, including Figure 5, are discussed and described in the text of the patent specification:

> In Step 3 of FIGS. 4, 5 and 6, the isolated target is ***non-specifically*** amplified to form a multitude of amplification products.

(*Id.* at col. 15, ll. 56-58, emphasis added.) Thus, Dr. Persing's contention that Example 5 teaches specific amplification is contrary to the description of the Figure associated with Example 5.

7. Further, use of the capture probe as a primer in Example 5 of the '338 Patent does not disclose amplification with specific primers. The addition of DNA polymerase and nucleoside-triphosphates would simply result in the extension of the capture probe DNA molecule by synthesis of a complement to the sequence of the target DNA not hydrogen-bonded to the capture probe. This extension would occur only once. Extension of the capture probe is not amplification of the target sequence. Because only a complement of the target would be synthesized, there is no amplification of the target sequence. It is also not clear from Example 5 that even extension of the capture probe using the target DNA as template would occur. If the capture probe was bound to the matrix through the 3' terminus such that its 5' end was free, there could be no extension. DNA polymerases require a '3-OH end to initiate extension.

8. One of ordinary skill would recognize that the nucleic acid extension in Example 5 would not be amplification, which is exponential and involves repeated steps. Using the target DNA as template would result in a one time, linear extension of the capture probe. The absence of a second specific probe means that there would be no amplification or further replication of the double-stranded DNA resulting from the DNA polymerase-catalyzed extension of the capture probe.

9. Dr. Persing's conclusion that Example 5 discloses specific amplification is incorrect because it is based on the incorrect assumption that the capture probe described in Example 5 "binds specifically to the target DNA." There is nothing in the 338 'patent that describes this capture probe as one that "binds specifically to the target DNA." Rather, Example 5 says that "denatured sample DNA is captured as described above". "Above" is Example 4, which simply

states that "A recA protein coated capture probe is then added to the digested target DNA . . . . The recA protein coated probe contains a nucleic acid sequence (a) that is homologous to a first target (a') sequence of the target DNA, as well as a homopolymer sequence on a capture bead." These passages do not state that the capture probe is specific to the target DNA. The fact that a probe is "homologous" does not mean that the probe is specific. "Homologous" has a very specific meaning in the art. Two sequences are "homologous" if one evolved from the other. "Homologous" does not mean that the two sequences are complementary over their entire lengths.

10. Even if the '338 specification contained a description of a specific capture probe which could be used as a primer (which it does not), then the result, as in paragraph 7, would be extension, not amplification. Further, even a very specific capture probe would likely function non-specifically as a primer under the very different reaction conditions of the processes of capture and extension. For example, the conditions necessary for extension would promote non-specific binding of the capture probe with the target DNA. Thus, the extension would be non-specific.

11. I have read Dr. Persing's comments regarding the prosecution history. These comments do not change any of the opinions that I expressed in my original report or in this report.

I hereby declare under penalty of perjury under the laws of the United States of America and the State of California that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. As discovery in this case is now just beginning, I reserve the right to change or supplement my opinion. This declaration was executed by me on this 1st day of June, 2001 at Blacksburg, Virginia.

Joseph O. Falkinham, III

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UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99CV2668 H (AJB)
THE HONORABLE MARILYN L. HUFF

REPLY DECLARATION OF CHRISTINE GRITZMACHER IN SUPPORT OF GEN-PROBE'S MOTION FOR PARTIAL SUMMARY JUDGMENT

Date: June 8, 2001
Time: 10:30 a.m.
Dept.: Courtroom 1

I, Christine Gritzmacher, declare as follows:

1. I am a member of the State Bar of California and admitted to practice before the United States Patent and Trademark Office.

2. I am employed as Patent Counsel by Gen-Probe Incorporated and I make this declaration in support of Gen-Probe's Motion for Partial Summary Judgment.

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3. Gen-Probe has obtained copies of the files of the United States Patent and Trademark Office concerning United States Patent No. 5,750,338 and United States Patent No. 5,714,380.

4. I reviewed the files referred to in paragraph 3. This declaration is based on that review. This declaration is prepared and offered pursuant to Rule 1006 of the Federal Rules of Evidence. The complete patent prosecution files are voluminous and cannot conveniently be examined in court in connection with Gen-Probe's Motion for Summary Judgment. I believe that copies of the individual patent documents referred to in this declaration have been previously submitted by the parties or are submitted as exhibits to accompanying reply notice of lodgment.

5. Vysis' first patent application claiming the combination of target capture and amplification was filed on December 21, 1987. (Vysis Exhibit A.) The claims of this application were rejected by Examiner Chambers. (Vysis Exhibit B.)

6. Vysis filed a "continuation" patent application on January 22, 1991 and the claims of that second application were also rejected by Examiner Chambers. (Vysis Exhibit C.)

7. Vysis filed yet another continuation application on September 14, 1992, leading to a third rejection by the same examiner in November 1992. (Vysis Exhibit D.) Because Vysis did not respond to the November 1992 rejection, the third patent application was abandoned as of February 5, 1993. (Exhibit 19 to Gen-Probe's Reply Notice of Lodgment.)

8. Vysis did not take any further steps to seek a patent for the invention of U.S. patent number 5,750,338 until May 3, 1994, more than one year after it abandoned its third application. In May 1994, Vysis petitioned the PTO to "revive" its third patent application. (Exhibit 20 to Gen-Probe's Reply Notice of Lodgment.) That petition was denied by the PTO on the ground Vysis had waited more than one year after abandonment to seek revival. (Exhibit 21 to Gen-Probe's Reply Notice of Lodgment.)

9. In May 1994, Vysis filed a *fourth* application, an identical copy of the three prior applications. While the prior three applications had all been assigned to the same patent examiner, the fourth application was assigned to a different examiner. On December 5, 1995, in prosecution of this fourth application, Vysis first suggested that the application encompassed methods of

specific amplification such as PCR. (Vysis Exhibit E.) That is, Vysis made this statement almost 8 years after the first patent application was filed.

10. Exhibit 22 to Gen-Probe's Reply Notice of Lodgment is a summary of the prosecution history of the '338 patent. I believe Exhibit 22 is an accurate summary of the information presented therein with respect to the prosecution history. This summary is prepared and offered pursuant to Rule 1006 of the Federal Rules of Evidence.

11. As used in this declaration, the term "Vysis" is used to refer collectively to the current patent owner, defendant Vysis, Inc., and to all of its predecessors in interest. The term "Vysis" includes Vysis' parent and predecessor in interest, BP Amoco Corporation.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed at San Diego, California on June 1, 2000.

Christine Gritzmacher

Christine Gritzmacher

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

vs.

VYSIS, INC.,

Defendant.

CASE NO. 99-CV- 2668 H (AJB)

Order Granting Motion for Partial Summary Judgment of Non-Infringement of the '338 Patent; Claim Construction of the term "Amplifying" as found in the '338 Patent

On March 13, 2001, plaintiff Gen-Probe, Incorporated filed a Second Amended Complaint for declaratory relief and unfair competition related to a patent and license agreement with the defendant Vysis, Incorporated. This case is styled as a declaratory judgment action brought by Gen-Probe. Thus, Vysis, the owner of U.S. Patent No. 5,750,338 ("the '338 patent"), is the defendant. Gen-Probe asks the Court to declare the '338 patent invalid and further declare that Gen-Probe's current and anticipated activities do not infringe any valid claims of the '338 patent. In its Second Amended Complaint, Gen-Probe asserts the following causes of action: (1) non-infringement of the '338 patent; (2) invalidity of the '338 patent; (3) declaratory relief; (4) unfair competition; (5) unenforceability of the '338 patent.

On April 30, 2001, Gen-Probe filed a motion for partial summary judgment under Counts One and Three of its Second Amended Complaint arguing that its nucleic acid test for human immunodeficiency virus ("HIV") and hepatitis C virus ("HCV") does not literally infringe the claims

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of the '338 patent held by Vysis. Specifically, Gen-Probe argues that the '338 patent describes and encompasses only methods of non-specific amplification and that its products do not incorporate non-specific amplification.

On May 25, 2001, Vysis filed its Opposition. On June 1, 2001, Gen-Probe filed its Reply. The Court held a hearing on the motion and claim construction for the term "amplifying," as found in Claims of the '338 Patent, on June 7, 2001. R. William Bowen and Stephen Swinton appeared on behalf of Gen-Probe and Charles Lipsey, John L'Estrange appeared on behalf of Vysis. Thomas Banks and Scott Orwell appeared telephonically on behalf of Vysis.

I. Scientific Background

The '338 patent relates generally to methods for use in nucleic acid diagnostics, including the use of nucleic acid "probes" to detect infectious organisms. The '338 patent describes methods by which nucleic acids may be "captured" onto solid supports and "amplified," so that small quantities of nucleic acids may be then detected by the probes.

"Target capture" techniques are used in nucleic acid methods to isolate a particular nucleic acid of interest prior to detection or other steps. In target capture methods, the target nucleic acid is bound to a solid support, such as a filter, particle, or bead, which allows the target to be removed from the sample in which it was originally contained.

In order to achieve a detectable level of target organisms in a sample, it is sometimes necessary to increase the target organism's nucleic acid through processes known as "nucleic acid amplification" by using enzymes and primers. "Polymerase" enzymes are used to copy a DNA or RNA strand and make its compliment. Primers are short pieces of DNA that are used in amplification methods to cause an enzyme, such as DNA polymerase, to start its copying at a certain point along a nucleic acid sequence. Like probes in the detection step, primers work by binding to a complementary nucleotide sequence in the target nucleic acid. Primers can either be specific or non-specific. Specific primers are designed to bind only to a pre-selected nucleic acid sequence. Non-specific or "random" primers can be used with DNA polymerase to copy random portions of the nucleic acid sequence of the target organism.

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II. The '338 Patent

The '338 patent contains six independent claims (claims 1, 7, 19, 27, 28, and 34). Each of these claims is generally directed to a method of, or kit for, capturing the target (i.e. binding a support to the target polynucleotide and substantially separating the support and bound target from the sample) and "amplifying" a target polynucleotide. Each independent claim contains the term "amplifying." For example, claim 1 provides:

> A method for amplifying a target polynucleotide contained in a sample comprising the steps of: (a) contracting the sample with a first support which binds to the target polynucleotide; (b) substantially separating the support and bound target polynucleotide from the sample; (c) amplifying the target polynucleotide.

The '338 patent specification sets forth seven examples of the methods taught by the inventors. The first three examples refer only to methods of target capture alone. Examples four through seven refer to combining target capture and methods of amplification.

III. Standard of Review

A. Motion for Summary Judgment

A motion for summary judgment shall be granted where "there is no genuine issue as to any material fact and . . . the moving party is entitled to judgment as a matter of law." Fed.R.Civ.P. 56(c); See also British Airways Bd. v. Boeing Co., 585 F.2d 946, 951 (9th Cir. 1978), cert. den., 440 U.S. 981 (1979). Determination of infringement is a two-step procedure. First, the claims are construed by the Court as a matter of law. Second, the properly construed claims are applied to the accused device, a question of fact. See Wang Laboratories, Inc. v. America Online, Inc., 197 F.3d 1377, 1380 (Fed. Cir. 1999); EMI Group North America, Inc. v. Intel Corp., 157 F.3d 887, 891 (Fed Cir. 1998).

B. Claim Construction

Claim construction is an issue of law to be decided by the Court. Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995), aff'd, 517 U.S. 370 (1996). "[T]he focus in construing disputed terms in claim language is not the subjective intent of the parties to the patent contract when they used a particular term. Rather the focus is on the objective test of what one of ordinary skill in the art at the time of the invention would have understood the term to mean." Id. at 985-86.

When construing the terms of a patent, the Court must first turn to "intrinsic evidence." Intrinsic evidence includes the claim itself, the specification, and the prosecution history of the patent. Vitronics Corp. v. Conceptronic, Inc., 90 F. 3d 1576, 1582 (Fed. Cir. 1996). Established rules of claim interpretation require that the Court first consider the words of the claims themselves, "both asserted and unasserted, to define the scope of the patented invention." Id. at 1582. The words are generally given their customary and ordinary meaning. Id.; Hoechst Celanese Corp. v. BP Chemicals, Ltd., 78 F.3d 1575, 1578 (Fed. Cir. 1996) (stating that in defining technical terms, the Court should interpret it "as having the meaning it would be given by persons experienced in the field of the invention"). However, the Court must follow the definition of terms intended by the patentee if his or her special definition is clearly delineated in the specification or file history. Vitronics Corp., 90 F.3d at 1583; Hoechst Celanese Corp., 78 F.3d at 1578.

The Court also considers the specification to determine whether the inventor has employed any terms or words in a manner that is inconsistent with their plain and ordinary meaning. Vitronics, 90 F.3d at 1582. "Claims must be read in view of the specification, of which they are a part." Markman, 52 F.3d at 979. "One purpose for examining the specification is to determine if the patentee has limited the scope of the claims." Watts v. XL Sys., Inc., 232 F.3d 877, 882 (Fed. Cir. 2000).

The Court also may review the prosecution history of the patent, if admitted into evidence. Vitronics, 90 F.3d at 1582. This history is "the complete record of all the proceedings before the Patent and Trademark Office, including any express representations made by the applicant regarding the scope of the claims." Id. It also includes prior art which is cited in the file history. Id. at 1583.

The Court may resort to extrinsic evidence only if the intrinsic evidence is considered and there still remains some ambiguity as to the scope or meaning of the claim. Id. at 1583. "[I]deally there should be no 'ambiguity' in claim language to one of ordinary skill in the art that would require resort to evidence outside the specification and prosecution history." Markman, 52 F.3d at 986. Extrinsic evidence can include any evidence outside the patent and prosecution history such as prior art documents, dictionaries, technical treatises, articles, expert testimony, and inventor testimony. Vitronics, 90 F.3d at 1584. However, "extrinsic evidence in general, and expert testimony in

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particular, may be used only to help the court come to the proper understanding of the claims; it may not be used to vary or contradict the claim language." Id.

IV. Analysis

Gen-Probe argues that it is entitled to summary judgment of non-infringement because its product (the HIV/HCV Assay) uses only specific amplification. Gen-Probe asserts that the term "amplifying" as used in the '338 patent would be understood by one of ordinary skill in the art at the time of the invention to encompass only non-specific amplification. Vysis agrees that Gen-Probe's product uses specific amplification. However, Vysis contends that the '338 patent is not limited to non-specific amplification.

A. Claim Construction

In construing the term "amplifying" of the '338 patent, the Court must first turn to "intrinsic evidence." Intrinsic evidence includes the claim itself, the specification, and the prosecution history of the patent. The claim language in this case does not help determine the construction of the term "amplifying." The term "amplifying" is found in each of the principle claims without any modification.

1. Specification

Gen-Probe argues that the specification of the '338 patent supports a construction of "amplifying" to only include non-specific amplification. The Court agrees. Immediately before the Examples that teach amplification in the '338 patent, the inventors set forth their teachings with respect to amplification methods.

> The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids. This can be achieved by **non-specific replication** using standard enzymes...In addition, where amplification is employed following purification of the target nucleic acids as described above, the amplified nucleic acids can be detected according to other, conventional methods not employing the [techniques] described above. Amplification of the target nucleic acid sequences, because it follows purification of the target sequences can employ **non-specific enzymes or primers** (i.e. enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence). Although any background, non-target nucleic acids are replicated along with target, this is not a problem because most of the background nucleic acids have been removed in the course of the capture process. Thus **no specially tailored primers are needed** for each test, and the same standard amplification reagents can be used regardless of the targets.

'338 patent, col. 30, lines 14-40 (emphasis added).

The introduction to the amplification techniques only addresses the possibility of using non-specific amplification methods. Vysis argues that the language permissive such that while "non-specific" methods "can be" used, they need not be. Vysis concedes that it did not invent specific or non-specific amplification. Rather, Vysis argues that its contribution to the science was the idea of target capture plus amplification. Vysis states that the patent focuses on the combination of the two, not describing amplification methods. Without target capture prior to amplification, non-specific amplification would not be a viable technique for detecting target nucleic acids in a sample. Vysis argues that the specification tells those of ordinary skill in the art that, while the use of target capture made it possible to use non-specific amplification in assays for detecting nucleic acids, the invention was more generally directed to the use of target capture prior to either specific or non-specific amplification. However, if the inventors wanted to teach that either method could be used they could have included at least one sentence or reference to specific amplification. They did not.

Vysis contends that a parenthetical sentence in Example 5 of the Specification does explicitly set forth the idea of specific amplification. The Specification of the '338 patent includes four Examples which teach the amplification techniques disclosed in the patent. Vysis agrees that Examples 4, 6 and 7 only teach non-specific amplification.[1] The parties dispute the proper interpretation of the description set forth in Example 5 of the Specification. Example 5 provides:

> In this example, both non-specific replication of target DNA and transcription of that DNA are used to amplify capture DNA. Referring to FIG. 5, ...Because the primers are random, some will, simple as a matter of statistics, bind to and cause replication of sample sequences, no matter what those sequences are. (Alternatively, the double stranded DNA can be formed by synthesis starting from capture probe a.)

'339 patent, col. 31, lines 24-26, 44-48.

Vysis contends that the parenthetical disclosure indicates that the capture probe is used as a specific primer to the target DNA and thus discloses "specific amplification." However, the explicit language of Example 5 (i.e. "non-specific replication" and "random" primers) refers only to non-specific amplification. In addition, Example 5 incorporates Figure 5, of the drawings in the patent.

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[1] For example, Example 4 describes a method of non-specific amplification using polymerases that lack transcriptional specificity ('338 Patent, col. 30, lines 59-68) and Example 6 describes amplification using random hexamer primers to "bring about non-specific double-stranded DNA synthesis." ('338 patent, col. 31, lines 57-64).

In discussing Figure 5, the inventors state, "In Step 3 of FIGS. 4, 5 and 6, the isolated target is non-specifically amplified to form a multitude of amplification products."

The words "specific amplification" or "PCR" do not appear in the Specification of the '338 patent. Vysis contends this is because the term "amplifying" was always used and meant to be used in its broadest sense, which includes both specific and non-specific amplification. However, the Federal Circuit has made clear that although the specification of a patent need not present every embodiment of the invention and the claims are not limited to the preferred embodiment of the invention, the claims can not enlarge what is patented beyond what the inventor has described as the invention. See Wang Laboratories, Inc. v. America Online, Inc., 197 F.3d 1377, 1383 (Fed. Cir. 1999); SciMed Systems, Inc. v. Advanced Cardiovascular Systems, Inc., 242 F.3d 1337, 1341 (Fed. Cir. 2001).

In Wang Labs, the Federal Circuit determined that although the term "frame" had meaning in general usage that encompassed both bit-mapped and character-based protocols, the specification only described and taught character-based display frames. Thus, the Court limited the claims to the only teaching set forth in the embodiment. In reaching its conclusion, the Court held that claims should not be interpreted to have a meaning or scope that would lead to their invalidity. Wang Labs, 197 F.3d at 1382-83. The Court held that the requirements of 35 U.S.C. § 112 (written description and enablement) could not be met with respect to protocols other than character-based frames. Id.

In this case, a motion for invalidity pursuant to 35 U.S.C. § 112 is not before the Court. However, the specification of the '338 patent does not describe specific amplification methods and does not teach any benefits from the combination of target capture and specific amplification. In fact, the specification teaches that you do not need to do specific amplification. The specification refers to specially tailored primers only to state that they are not necessary when an initial target capture step is used. In addition, Example 5 teaches non-specific replication of target DNA using random primers and non-specific transcription. The parenthetical reference to an "alternative" method, does not teach that such a method constitutes specific amplification or that the capture probe functions as a specific primer. The plain reading of Example 5 and Figure 5 is that they teach non-specific amplification. The Court will try to construe claims, when feasible, to sustain their validity. The Court finds it

difficult to construe "amplifying" to include specific amplification based on the disclosures in the specification that would satisfy the written description requirement of 35 U.S.C. § 112.

Recently the Federal Circuit in SciMed Systems stated, "[w]here the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims, read without reference to the specification, might be considered broad enough to encompass the feature in question." SciMed, 242 F.3d at 1341. The Court concludes that the specification supports Gen-Probe's contention that the term "amplifying" as used in the '338 patent only encompasses non-specific amplification.

2. Prosecution History

Vysis contends that the prosecution history makes clear that both the patent owner and the PTO considered the claimed invention to include PCR, a type of specific amplification. The original claims of the '338 patent were rejected by the PTO, citing the PCR patents. Vysis argues that this must mean that the PTO understood the '338 patent to include specific amplification techniques. Vysis also points to a response by the patent owner to the PTO, indicating that "[t]argets can be amplified by a number of ways including PCR." Banks Decl., Ex. E, p. 18. Finally, in the Examiner's Statement of Reasons for Allowance the Patent Examiner states, "[t]he claims are drawn to methods of PCR amplification wherein the target is first separated from the sample by using a support that binds to the target polynucleotide and then amplified." Banks Decl., Ex. F, p. 2.

Vysis argues that the Patent Examiner's understanding of the meaning of patent claims developed during prosecution is relevant to construing the proper scope and meaning of those terms. See Markman, 52 F.3d. At 983.

Gen-Probe asserts that the rejection by the PTO of the patent application based on the Mullis (PCR) patent does not support the claim that the patent covered PCR amplification methods. Vysis acknowledged in oral argument that did not have a license to the Mullis patents or PCR method. Gen-Probe argues that the patent application was rejected as obvious in light of the PCR patents because specific capture methods plus non-specific amplification were an attempt to achieve the same results as PCR. Gen-Probe also contends that statements made by the patent owner to the Patent Examiner in 1995, eight years after the application was first filed, were made too late to determine how a person

skilled in the art would have understood the invention as of the date of filing.

The focus of claim construction is how a person skilled in the art would have understood the claimed invention in the patent at the time of filing. Markman, 52 F.3d at 985-986. The prosecution history indicates that the patent application was rejected at least three times by the PTO for being obvious in light of a combination of target capture and amplification patents, including the Mullis (PCR) patents. However, despite the fact that the patent owner was clearly aware PCR, it failed to explicitly include specific amplification methods in the teachings of the patent. The prosecution history does not help explain this omission.

The Court concludes that the references to the Mullis patents and PCR in the prosecution history do not help clarify the proper construction of the term "amplifying" as used in the '338 patent. At most, the prosecution history indicates that the idea of amplification by first using specific target capture techniques is close enough to the goals of PCR to be "obvious" to the PTO in light of the Mullis patents.[2]

3. Extrinsic Evidence

Gen-Probe argues that the inventor's own testimony about the scope and intent of the patent confirms that "amplifying" includes only non-specific amplification. The Court only uses extrinsic evidence to help it come to the proper understanding of the claim terms. The Court will not use extrinsic evidence to vary or contradict claim terms. See Vitronics, 90 F.3d at 1584.

Gen-Probe has submitted testimonial and documentary evidence from the inventors of the '338 patent. Gen-Probe highlights the testimony of inventor Jon Lawrie. Lawrie stated that the '338 patent, "was directed to methods separate from PCR." Lawrie Depo. at 178:19-180:11. Similarly, inventor Walter King testified that specific amplification was not discussed at the meeting of the inventors in 1986 because the objective was to find an alternative to PCR. King Depo. at 184-186. King stated, "I think that at the highest level we were looking for amplification methods that did not involve PCR amplification." King Depo. at 45:10-15. King also testified that he did not understand the inventors

[2] In addition, an early drawing by inventor Jon Lawrie indicates that he was concerned that the use of "specific capture and non-specific amplification" was "too close" to the PCR method invented by Mullis and others at Cetus Corp. (Exh. 12).

to be claiming as their invention a combination of target capture and specific amplification. King Depo. at 136:14-21.

Gen-Probe also points to a letter written by Dr. James Richards, Director of Business Development and Licensing for Gene-Trak Systems, to one of Gene-Trak's partners stating:

> Cetus, Sibia/Salk, Biotechnica, etc. all claim specific primers for amplification whereas the present invention claims uses of the opposite, namely non-specific primer or promoters...Following extensive washing, captured target polynucleotides could be released and the non-specific amplification process could take place.

Jaczko Decl., Ex. 1, pg. 2.

Vysis argues that the testimony former employees of Vysis' predecessor company Gene-Trak Systems should be given no weight because there can be "significant difference between what an inventor thinks his patented invention is and what the ultimate scope of the claims is after allowance by the PTO." Markman, 52 F.3d at 985. However, Vysis' argument is more appropriately raised when inventor try to expand the scope of the patent claims by testifying about their subjective intent, over the description set forth in the specification. In this case, the specification supports a construction of the term "amplifying" to include only non-specific amplification and the inventors' testimony supports this construction.

While the Court does not use extrinsic evidence to construe claim terms, the evidence offered by Gen-Probe helps explain the context of the '338 patent. In particular, the inventor's testimony and the Richards' letter explain why there is no explicit reference in the specification to amplification using PCR. The extrinsic evidence in this case supports the conclusion that one of ordinary skill in the art at the time of the invention would have understood the term "amplifying" to mean non-specific amplification.

Based on the explicit language of the specification, the repeated reference to non-specific amplification methods, and the absence of any reference to specific amplification or PCR, the Court construes the term "amplifying" as found in the claims of the '338 patent to encompass only non-specific amplification. The Court finds that one of ordinary skill in the art as of December 1987 would have understood from the specification that the inventors' method combined target capture and non-specific amplification. This conclusion is reinforced by the inventors' testimony and the Richards' letter.

B. Infringement

After construing the term "amplifying" the Court can turn to question of literal infringement. Literal infringement requires that the accused device contain each limitation of the claim. Bayer AG v. Elan Pharm. Research Corp., 212 F.3d 1241, 1247 (Fed. Cir. 2000). In this case, Gen-Probe's Assay uses a target-specific amplification technology. Vysis admits that Gen-Probe's product uses specific amplification. There is no issue of material fact which would prevent the Court from ruling on infringement in a motion for summary judgment. Since the Court has construed the term "amplifying" to encompass only non-specific amplification, the Court concludes that Gen-Probe does not literally infringe the claims of the '338 patent.

V. Conclusion

For the reasons set forth above, the Court GRANTS Gen-Probe's Motion for Partial Summary Judgement of non-infringement of the claims of the '338 patent.

IT IS SO ORDERED.

DATED: 6/19/01

Marilyn L. Huff

MARILYN L. HUFF, Chief Judge
UNITED STATES DISTRICT COURT

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